STATISTICAL ANALYSIS PLAN

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Study Number:	Study 0128
Study Title:	A Phase 3, 52-week, Randomized, Active-Controlled Parallel Group Study to Evaluate the Safety and Tolerability of Nebulized TD-4208 in Subjects with Chronic Obstructive Pulmonary Disease
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STATISTICAL ANALYSIS PLAN

revefenacin, Study 0128

A Phase 3, 52-week, Randomized, Active-Controlled Parallel-Group Study to Evaluate the Safety and Tolerability of Nebulized TD-4208 in Subjects with Chronic Obstructive Pulmonary Disease

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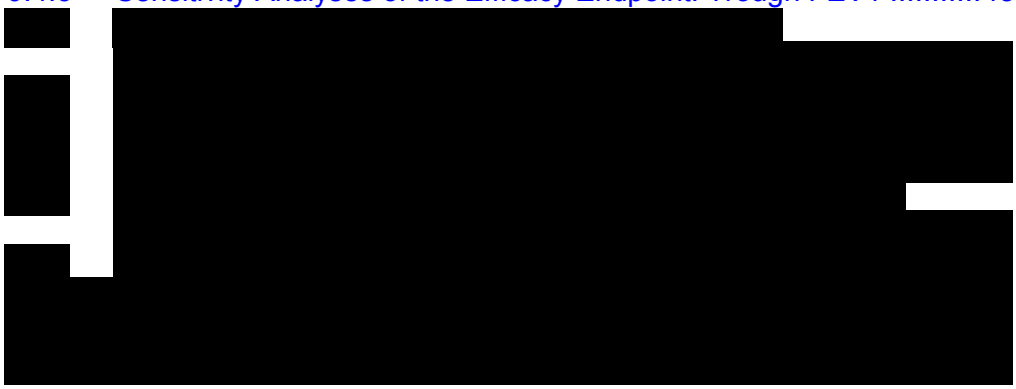

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ABS	absolute
ADaM	Analysis data model
AE	adverse event
ALB	albuterol
AUC	area under the curve
AR	autoregressive
BDI	Baseline Dyspnea Index
BID	twice-daily
BLQ	below level of quantification
BLS MEAN	Binomial least square mean reporting method
BMI	body mass index
BP	blood pressure
CAT	COPD Assessment Tool
CCQ	Clinical COPD Questionnaire
CEC	cardiovascular event committee
CFB	change from baseline
CI	confidence interval
C	continuous reporting method
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CSR	clinical study report
D	day(s)
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ePFM	electronic peak flow meter
F	frequency reporting method
FVC	forced vital capacity
FEV_1	forced expiratory volume in one second
GERD	gastrointestinal reflux disease
GOLD	Global initiative for chronic obstructive lung disease
H	hour(s)
HR	heart rate
ICS	inhaled corticosteroid
IPR	ipratropium
ITT	intent-to-treat
KDE	kernel density estimation
KM	Kaplan Meier reporting method

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
LOD	limit of detection
LS	least-square
MAR	missing at random
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MF	multiple frequency reporting method
mL	milliliters
mMRC	Modified Medical Research Council Dyspnea Scale
MNAR	missing not at random
NC	non-calculable
NLS MEAN	normal least square mean reporting method
NQ	non-quantifiable
OTE	overall treatment effect
PD	pre-dose
PK	pharmacokinetic
PP	per-protocol
QD	once-daily
REV	revefenacin
RMMM	repeated measures mixed effect model
SAE	serious adverse event
SAP	statistical analysis plan
SCR	screening
SGRQ	Saint Georges Respiratory Questionnaire
SOC	system organ class
TDI	Transitional Dyspnea Index
TEAE	treatment-emergent adverse event
UN	unstructured
WM	weighted mean
WHODD	World Health Organization Drug dictionary

1 INTRODUCTION

This document outlines the initial plan for the summarization and analysis of clinical data collected in the Phase 3 Study 0128 for revefenacin. This document describes the a priori plan for analysis. Once the analysis is in progress, it may become apparent from the data that the planned analysis should be modified. Any substantive modification to the original analysis plan will be identified in the clinical study report (CSR).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is:

- To characterize the safety and tolerability of TD-4208 administered once daily for 52 weeks in a population of subjects with moderate to very severe COPD.

2.2 Exploratory Objectives

[redacted]

3 OVERVIEW OF STUDY DESIGN

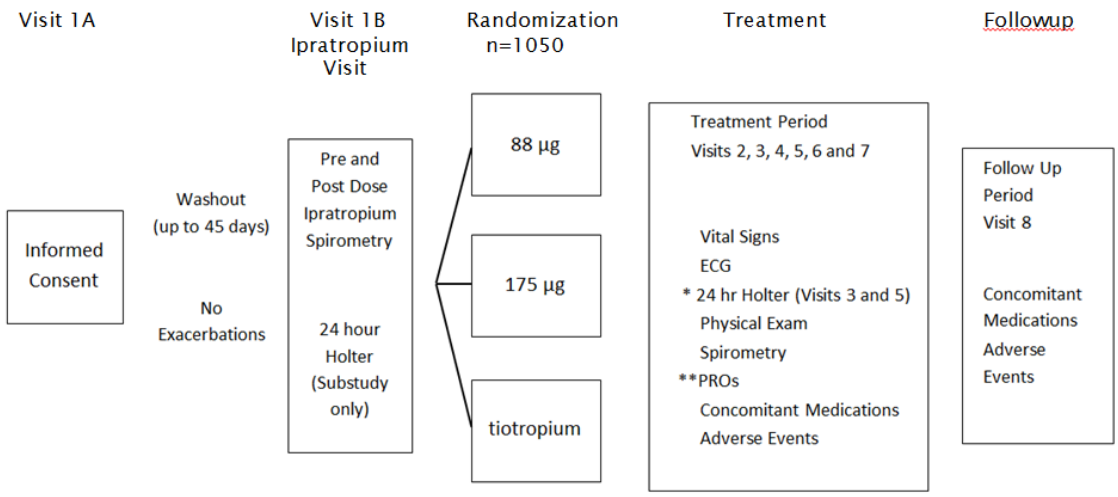
Studies 0128 is a randomized, active-controlled, parallel-group study. Each subject will receive treatment once daily in the morning for a total of 52 weeks. There will be three treatment groups (TD-4208 88 µg, TD-4208 175 µg, and tiotropium 18 µg). TD-4208 will be administered as a 3 mL solution by inhalation using the [redacted] jet nebulizer and tiotropium as a dry powder capsules with the [redacted] device. The study will be double-blind with respect to the TD-4208 dose arms, and open-label with respect to the tiotropium control arm. There will be 1050 subjects randomized with the intention to obtain data on the final day of the treatment period (Day 365) from [redacted] Screening will ensure that subjects are eligible for inclusion in the study. Subjects will undergo washout from prohibited medications as appropriate, including all products containing long-acting antimuscarinics [LAMA] (either in combination or alone). Patients who are currently on long-acting beta-agonists [LABA] (with or without inhaled corticosteroids) will be permitted to be enrolled in the study. Subjects that are not on a LABA or LABA / ICS when they enter the study and require a LABA or LABA/ICS to treat a COPD exacerbation at the discretion of the investigator in accordance with COPD guidelines will be allowed to remain in the study.

Screening will ensure that subjects are eligible for inclusion in the study. Subjects will undergo washout from prohibited medications as appropriate, including all products containing long-acting antimuscarinics [LAMA] (either in combination or alone). Patients who are currently on long-acting beta-agonists [LABA] (with or without inhaled corticosteroids) will be permitted to be enrolled in the study. Subjects that are not on a LABA or LABA / ICS when they enter the study and require a LABA or LABA/ICS to treat a COPD exacerbation at the discretion of the investigator in accordance with COPD guidelines will be allowed to remain in the study.

[redacted]

The study will consist of 1 or 2 screening visits, depending on whether a washout period is required and 6 treatment period visits and a telephone follow-up visit as shown in the study design schematic (Figure 1).

Figure 1: Study Schematic



4 SAMPLE SIZE AND POWER

Sample size (n=350 per group) is based on meeting ICH regulatory requirements for long-term safety for chronic use in this indication. [redacted]

5 STUDY ENDPOINTS

All study endpoints and/or assessments include an evaluation type, i.e., absolute value, change from baseline, an ADAM Type, either derived from raw data or raw data, i.e., CRF or Lab-type data, an evaluation window, i.e., screening, Day 1, Days 1-365, and a summary type, i.e., continuous, frequency, normal least squares.

The primary endpoint(s) of this study assess the long-term safety and tolerability of TD-4208 in the treatment of COPD:

- Frequency and severity of adverse events, including exacerbations
- Vital signs

- Clinical laboratory evaluations
- 12-lead ECG changes from baseline

The exploratory endpoints will be characterized:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.1 General Endpoints

The following general endpoints will be summarized in Table 1.

Table 1: General Endpoints

Endpoint	Evaluation Type	ADAM Type	Reporting Window	Summary Type(s)
age	[redacted]			
sex				
ethnicity				
race				
height				
weight				
BMI				
smoking Status				
Maximum number of packs per day				
Number of years smoked				
Number of pack-years				
Age (≤65, >65)				
concurrent ICS use				
concurrent LABA use				
concurrent QD/BID/NO LABA				
concurrent ICS/LABA use				
Baseline FEV_1				
predicted normal FEV_1				
percent predicted FEV_1				
Baseline FVC				
FEV_1 to FVC ratio				
duration of COPD				
number of exacerbations in last 12 months				
number of hospitalization for exacerbation in last 12 months				
subjects with a history of respiratory infections				
subjects with a history of supplemental oxygen				
subjects with a history of diabetes mellitus				
subjects with a history of pulmonary hypertension				

Table 1: General Endpoints

Endpoint	Evaluation Type	ADAM Type	Reporting Window	Summary Type(s)
subjects with a history of ischemic heart disease	[redacted]			
subjects with a history of GERD				
subjects with cardiovascular risk factors				
GOLD category				
GOLD severity of airflow limitation				
Indicator: Baseline CAT Score: CAT ≥10				
Indicator: mMRC score ≥2				
primary reason for study drug discontinuation				
subject disposition				
subjects in Safety Group				
subjects in ITT Group				
subjects in PP Group				

Note: D: day, PD: pre-dose, SCR: screening, ABS: absolute value, EOS: end of study
Note: For summary types, see Appendix 1

5.2 Safety Endpoints

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology, chemistry, and urinalysis), corrected QT interval (QTc, from standard safety digital ECGs) and exacerbation data. Vital signs will be summarized in terms of observed values and changes from baseline.

Cardiovascular events of interest will be specified in a separate CEC charter.

In addition, the rate of exacerbations through adverse events and [redacted] will be summarized.

Table 2: Additional Safety Endpoints

Endpoint	Evaluation Type	ADaM Type	Reporting Window	Summary Type(s)
Time to first exacerbation_AE	OBS	derived	D1-365	KM
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.3 Exploratory Efficacy Endpoints

Endpoint	Evaluation Type	ADAM Type	Reporting Window	Summary Type(s)
[redacted]				

Endpoint	Evaluation Type	ADAM Type	Reporting Window	Summary Type(s)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

6 GENERAL ANALYSIS CONSIDERATIONS

6.1 Global Definitions and Conventions

All data from scheduled and unscheduled visits will be presented in the subject listings; however, unless noted otherwise, only data from appropriately windowed visits (Section 6.1.2) will be included in the summaries, statistical analysis, and calculation of derived parameters.

6.1.1 Baseline Definition

The Table 3 indicates the timing of the baseline assessment to be used in the analysis of specific parameters.

Table 3: Baseline Assessment for Specific Parameters

Parameter	No Baseline	Visit 1B	Visit 2 (Day 1-PD)	PD of each visit
Laboratory safety tests		X		
Vital signs and ECG			X	
Holter ECG		X		
FEV_1			X[1]	
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]			[redacted]	
[redacted]			[redacted]	
[redacted]			[redacted]	
[redacted]			[redacted]	

1 mean of -45 and -15 min PD assessments

6.1.2 Analysis Windows

All assessments will be summarized using analysis windows.

Instances may occur where a subject is administered pre-dose assessments, e.g., PROs, on planned Day 1 [Visit 2] but then the subject does not dose due to various reasons. Since the subject will dose at an eventual later date, the current date would be assigned a study day <1 since study days are relative to first dose. The subject will, in general, not repeat the PRO assessments. These assessments (study day <1) will be windowed into study day 1 [Visit 2] for analysis and summary purposes.

In the instance where the PROs are repeated, the study day <1 will be windowed as unscheduled and the Study Day 1 will be windowed as Study Day 1.

All data (scheduled and unscheduled visits) will be presented in the subject listings; however, unless noted otherwise, only data from assessments within analysis windows will be included in the summaries, statistical analysis, and calculation of derived parameters.

The following visit windows will be used in the summary of clinical data.

Table 4: Analysis Windows: Visits

Nominal Visit	Nominal Day	Start (days)	Stop (days)
2	1	1	1
3	29	19	39
4	92	72	112
5	183	153	213
6	274	244	304
7	365	335	395
8	NA	V7+5	V7+9

Safety Endpoints

The following windows summarize the definition of treatment-emergent.

Table 5: Analysis Windows: Treatment Emergent Events

Window	Start	Stop
Adverse events	Signing of ICF	Maximum of Follow-up visit or Last dose + 7 days
Treatment-emergent Adverse events, ECGs and Labs	Post first dose	Last dose + 7 days

Table 6: Analysis Windows: Vital Signs and ECGs

Amendment	Window	Start	Stop
Amendment 3	“60 minutes pre-dose” / “pre-dose”	-90	-30
Amendment 3	“10 min post dose”	5	40

General Selection Process for Multiple Records in an Analysis Window

In general, if multiple, valid, non-missing observations exist at a visit or collection time point then records will be chosen based on the following:

- The record closest to the nominal time point in question, or,
- The later record if the two visits are equidistant from the time point, or,
- The average (arithmetic mean) if there is more than one record at the time point (generally applies to assessments done in triplicate).

Multiple Spirometry Records

If multiple spirometry non-NULL records exist, the later record by date/time will be selected.

Spirometry records with a NULL value will be excluded from analyses.

6.1.3 Evaluable Efficacy Assessment

Potential Confounders to Efficacy Assessment

There’s no formal statistical comparison on exploratory efficacy assessment between revefenacin and tiotropium in this safety study.

Additional concomitant short acting bronchodilators or restricted long-acting muscarinic antagonists or beta agonists, taken immediately prior to or during efficacy assessments will confound the assessment of a treatment effect attributed to revefenacin relative to tiotropium. In addition, the lack of administration of study drug, e.g., subjects who have discontinued study drug prior to an assessment or subjects who did not dose on the study day, will confound the assessment of the treatment effect of revefenacin relative to tiotropium.

[redacted]

6.1.4 Missing Data

In general, it is not anticipated that there will be considerable missing data. In general, missing data will not be imputed. Missing data for the following specific endpoints will be handled as follows:

Exploratory Efficacy Endpoint

[redacted]

Adverse Events

For graded adverse event summaries, subjects with an AE and no grade on the CRF will be graded as severe.

For graded adverse event summaries, subjects with an AE and no relatedness on the CRF will be graded as "possibly/probably related".

Concomitant Medications

Missing dates and times will be handled as follows:

- Missing start date (no month or year) will be considered as taken on the first dose date;
- Missing start day will be taken as the first day of the month;
- Missing start month will be taken as January;
- Missing stop date will be considered as taken during the entire remaining study period.
- If a start or stop time is missing, the start time is imputed as 1 minute after a.m. midnight (12:01) and stop time is imputed to be 1 min before p.m. midnight (23:59).

Laboratory Data

For non-efficacy laboratory data, a missing baseline value will be replaced with the last available assessment, generally the screening assessment. A retest value will be used if the first test is invalidated, e.g., specimen hemolyzed.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation/limit of detection (LOD) will be, in general, imputed as follows:

- A value that is 1 unit less than the LOD will be used for calculation of descriptive statistics if the data are reported in the form of "<x" (x is considered as the LOD). More specifically, x−1 is used for data summarization if the data are reported in the form of "<x"; and x.e where e = d−1, will be used for analysis if the data are reported in the form of "<x.d".
- The LOD will be used for calculation of descriptive statistics if the data is reported in the form of "≤x" or "≥x".

6.2 Adverse Events

Recorded adverse events will be mapped according to the MedDRA thesaurus by the data management CRO for this study, with Theravance review and approval of the mappings. [redacted] will use MedDRA, version 18.1.

6.3 Medications

Recorded prior and concomitant medication names will be mapped according to the World Health Organization Drug Dictionary (WHODD) by the data management CRO for this study with Theravance Biopharma review and approval of the mappings. The CRO will use the September 2015 version of the WHODD.

For non-concomitant medication eCRFs that contain albuterol use information, e.g., study drug administration and in-clinic albuterol dosing forms, mapping will be conducted by Theravance Biopharma using the WHODD mapping for salbutamol.

6.4 Medical History

Medical history will be mapped according to MedDRA version 18.1 and will be provided in listings. Selected medical history will be summarized.

6.5 General Considerations for Summaries

Analyses and tabulations will generally be prepared using SAS®, version 9.4 or later.

Reporting Structures for Data Summary

Data will be summarized using the appropriate reporting structure as defined in Appendix 1.

Presenting Multiple Summaries on Same Table Summary

In summary tables where multiple single line frequency summaries are being presented, the "n line" can be suppressed in the individual summaries and presented at the top of the summary a single time.

Use of Evaluable N Terminology

The term "evaluable non-missing n" will only be used in summaries derived from model-based analyses.

Ordering of Treatment Headers in Summary Tables

In summary table treatment headers, reverencing will be abbreviated as REV and will be presented in the following order:

- Tiotropium,
- REV 88 mcg,
- REV 175 mcg,
- Total (Applicable to General Analysis and Exposure summaries).

In safety summaries by LABA subgroup, treatment groups will be presented in the following order:

- Tiotropium,
- Tiotropium + ICS/LABA and/or LABA
- REV 88 mcg,
- REV 88 mcg + ICS/LABA and/or LABA
- REV 175 mcg,
- REV 175 mcg + ICS/LABA and/or LABA.

Rounding

In general, the convention for rounding is as follows:

- Values greater than or equal to x.x5 are rounded up,
- Values between 0 and less than x.x5 are rounded down,
- Values between –x.x5 and 0 are rounded up,
- Values less than or equal to –x.x5 are rounded down.

All rounding will occur in the last step of data summarization.

Significant Digits

Raw measurements will be reported the same as the data captured electronically or on the CRFs. Exceptions will be made for values reported with greater than four significant digits (round to four significant digits using a similar criterion as for percentages with the five in the last digit).

The following significant digit convention will be used for the purposes of summarizing efficacy data:

- Mean, median: 1 significant digit,
- Standard deviation: 2 significant digits,
- Minimum, maximum: 1 significant digit,
- Percentages: 1 decimal place.

The following significant digit convention will be used for the purposes of summarizing non-efficacy data (primarily lab data) data:

- Mean, median: +1 significant digit reported data,
- Standard deviation: +2 significant digits reported data,
- Minimum, maximum: 2 significant digits reported data,
- Percentages: +1 decimal place.

P-values

P-values will be reported with four significant digits, e.g., 0.xxxx, except when reporting p-values less than 0.001, reported as <0.001.

Colors in Figures

In figures that only contain the three treatment groups, the following colors will be used:

- Tiotropium (orange),
- revefenacin 88 mcg (steelblue – CX4682B4),
- revefenacin 175 mcg (dodgerblue- CX1E90FF).

In figures that contain multiple subgroups in the same figure (e.g., forest plots), no color (default black) will be used.

6.6 Tables, Figures and Listings (TFLs)

A line listing of tables, listings, and figures to be generated are in Appendix 15.

Table titles will be denoted as underlined text in the SAP.

Selected table, listing or figure mock-ups will be in a separate document.

7 ANALYSIS SETS

7.1 Safety

The Safety analysis set will include all subjects who

(1) Were randomized into the study, and,

(2) Received at least one dose of study drug (revefenacin or tiotropium).

Treatment assignment will be based on actual treatment. The Safety analysis set is the primary analysis set for safety analyses.

7.2 Intent-to-Treat

The Intent-to-treat (ITT) analysis set will include all subjects who

(1) Were randomized into the study,

(2) Received at least one dose of study drug (revefenacin or tiotropium), and,

(3) Have at least one recorded post-baseline FEV_1 assessment.

Treatment assignment will be based on the treatment randomized. [redacted]

7.3 Per-Protocol

The Per-protocol (PP) analysis set included all subjects in the ITT analysis set with no major analysis protocol deviations (Section 7.5).

Treatment assignment will be based on actual treatment.

7.4 Examination of Subgroups

7.4.1 Study-Specific Subgroups

The following subgroups are pre-defined for the purposes of analyses:

1. Baseline smoking status: [redacted]
2. Age: [redacted]
3. Current ICS use: [redacted];
4. Reversibility to a short-acting bronchodilator:

   [redacted]
5. Baseline post bronchodilator % predicted FEV_1: [redacted]

7.5 Major Analysis Protocol Deviations

Major analysis protocol deviations that could potentially affect the efficacy conclusions of the study will be identified prior to database lock. Major analysis protocol deviations may include, but are not limited to:

- [redacted]

Subjects with major analysis protocol deviations will be identified before the database lock and provided in a listing.

In addition, a listing of all major deviations will be provided whether or not they impact the analysis.

8 DEFINITION OF ANALYSIS VARIABLES

8.1 General Variables

Age

Age will be calculated as of the date of signing informed consent and truncated to its integer value. The following formula is used:

$$Baseline\ Age = floor\left(\frac{Date\ of\ Informed\ Consent - Date\ of\ Birth}{365.25}\right).$$

BMI

BMI will be calculated and converted to metric units by the following:

$$BMI_{\left(kg/m^2\right)} = \frac{weight(kg)}{\left(height(m)\right)^2}.$$

Reversibility to a Short-Acting Bronchodilator

Reversibility (yes or no), to ipratropium, is defined as a post-bronchodilator (CFB) FEV_1 increase of at least (≥) 12% and at least (≥) a 200 mL increase, relative to the pre-bronchodilator FEV_1, at the relative screening visit.

Smoking Pack Years

Maximum number of packs multiplied by years smoked.

LABA Use and Type of LABA Use

Two variables will be used in the analysis models to identify if a subject was on a concurrent LABA or ICS/LABA medication and whether the concurrent LABA or ICS/LABA was administered QD or BID:

- Concurrent LABA: yes (1) or no (0)
- LABA Type: none (0), QD (1) or BID (2)

LABA flags will be derived using concomitant medication data, i.e., presence or absence of a record matching the logic for LABA use, to ensure accuracy.

Table 7: Dummy Coding for Concurrent LABA

LABA group	Concurrent LABA	LABA Type
No concurrent LABA	0	0
Concurrent QD LABA	1	1
Concurrent BID LABA	1	2

GOLD Severity of Airflow Limitation Categories

Table 8: GOLD Severity of Airflow Limitation Categories

GOLD airflow category	Severity	FEV_1 threshold
GOLD 1	Mild	≥80% predicted
GOLD 2	Moderate	≥50%, <80% predicted
GOLD 3	Severe	≥30%, <50% predicted
GOLD 4	Very severe	<30% predicted

Note: Based on post-ipratropium values in patients with post-ipratropium FEV1/ FVC <0.70

Screening data will be used to categorize subjects.

GOLD Categories (2011 Definition)

Table 9: GOLD Categories

Category	Characteristic	GOLD Airflow Severity Category	Exacerbations	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤1	0-1	<10
B	Low Risk More Symptoms	GOLD 1-2	≤1	≥2	≥10
C	High Risk Less Symptoms	GOLD 3-4	≥2	0-1	<10
D	High Risk More Symptoms	GOLD 3-4	≥2	≥2	≥10

Screening data will be used to categorize subjects. For the purposes of categorization, GOLD categories (using 2011 definition to ensure consistency between the efficacy and safety studies in the phase 3 program) will use the GOLD airflow severity category and CAT scores as the primary method to determine GOLD Category. If GOLD airflow severity is missing, then exacerbations will be used. If CAT score is missing, then mMRC score will be used.

8.2 Exploratory Efficacy Variables

[redacted]

[redacted]

9 ANALYSES

Table, figures and listing titles are denoted in underlined text.

9.1 Safety Variables

Adverse Events

Adverse events (AEs) are recorded from signing of the informed consent form through the final follow-up assessment. Non-treatment-emergent AEs and treatment-emergent AEs will be summarized separately.

Bronchodilators by Drug Class

Appendix 3 contains coding logic for determination of specific drug classes for bronchodilators.

[redacted]

9.2 General Analyses

9.2.1 Subject Disposition

Subject disposition information will be summarized for all subjects by treatment group. Summaries will include the following parameters:

- Number of randomized subjects,
- Number and percentage of subjects randomized and treated with study drug (ITT Analysis set),
- Number of subjects randomized, but not dosed
- Number and percentage of subjects completing the study,
- Number and percentage of subjects by reason discontinuing the study drug,
- Number and percentage of subjects by reason discontinuing the study.

A listing of subject disposition will include the ITT analysis set status, the date of informed consent signed, the date of first dose and last dose of study drug, primary reason for subject discontinuation of study medication, the date of last visit, study completion status, primary reason for study termination, and the date of last contact.

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, height, weight, and BMI) will be summarized for the safety analysis set.

A listing of demographics and baseline characteristics will also be provided.

9.2.3 Reversibility Summaries

A post-bronchodilator screening reversibility summary taken during screening visits will be provided with the following parameters:

- Ipratropium reversibility (mL),
- Ipratropium reversibility (%),

In addition, a post-bronchodilator screening reversibility categorical summary will be provided in a separate summary:

- Not reversible to ipratropium,
- Reversible to ipratropium,

Separate listings will also be provided. The ITT analysis set will be used for the summaries.

9.2.4 Screening and Baseline Spirometry Summaries

A screening spirometry summary will be provided with the following parameters:

- Post-ipratropium predicted Normal FEV_1 (mL),
- Post-ipratropium percent predicted FEV_1 (%),
- Post-ipratropium FEV_1 (mL),
- Post-ipratropium FVC (mL),
- Post-ipratropium FEV_1 to FVC (ratio),

A Baseline spirometry summary will be provided in a separate table with the following parameters:

- Baseline FEV_1 (mL),
- Baseline FVC (mL),
- Baseline FEV_1 to FVC (ratio),
- Baseline predicted Normal FEV_1 (mL),
- Baseline percent predicted FEV_1 (mL),

A single listing that includes screening, baseline and post-baseline spirometry will be provided. The ITT analysis set will be used for the summaries.

9.2.5 Baseline Clinical Characteristics Summaries

A summary of COPD clinical characteristics taken at baseline will be provided with the following parameters:

- Proportion of subject ≥65 years of age (%),
- Duration of COPD (years),
- Number of exacerbations in past 12 months (%),
- Number of hospitalizations for an exacerbation in past 12 months (%),
- Proportion of subjects with a history of respiratory infections (%),
- Proportion of subjects with a history of supplemental oxygen use (%),
- Proportion of subjects with diabetes mellitus (%),
- Proportion of subjects with a history of pulmonary hypertension (%),
- Proportion of subjects with a history of ischemic heart disease (%),
- Proportion of subjects with a history of GERD (%),
- Proportion of subjects with a cardiovascular risk factor (%).

A summary of smoking characteristics taken at baseline will be provided with the following parameters:

- Smoking history, current and former, (%),
- Number of years smoked (years),
- Maximum number of packs per day (packs),
- Pack years (packs).

A summary of LABA and ICS use will be provided with the following parameters using coded concomitant medication data:

- Concurrent ICS use (%),
- Concurrent LABA use (%),
- Subgroup: Concurrent QD LABA use (%),
- Subgroup: Concurrent BID LABA use (%),
- Concurrent ICS/LABA use (%).

Three listings will also be provided. The ITT analysis set will be used for the summaries.

9.2.6 GOLD Category Summary

A summary of GOLD categories will be provided with the following parameters:

- GOLD Severity of Airflow Limitation groups,
- GOLD Categories.

A listing will be provided. The ITT analysis set will be used for the summary.

9.2.7 Key Demographic and Baseline Characteristics Summary

A summary of key demographic and baseline characteristics will include the following with the following parameters on a single page:

- Age, mean(SD),
- Sex (male), %,
- Race (white), %,
- BMI, mean (SD),

- Current smoker (yes), %,
- Concurrent ICS use (yes), %,
- Concurrent LABA use (yes), %,
- Concurrent ICS/LABA use (yes), %,
- Post-ipratropium percent predicted FEV_1, mean (SD),
- Post-ipratropium FEV_1 to FVC (ratio), mean (SD),
- Baseline FEV_1 (in mL), mean (SD),
- Proportion of subjects with baseline mMRC ≥2, %
- Proportion of subjects with baseline CAT ≥10,%
- Proportion of subjects with ≤1 exacerbations in prior year, %
- GOLD C/B categories, n %
- BDI score, LS mean (SE)

For continuous summaries, only the "mean (SD)" will be displayed. As this data is summarized in list format elsewhere, no listing is provided for this summary. The ITT analysis set will be used for the summary.

9.3 Safety Analyses

For all safety analyses, the safety analysis population will be used.

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology, chemistry, and urinalysis), corrected QT interval (QTc, from standard safety digital ECGs) and exacerbation data. Vital signs will be summarized in terms of observed values and changes from baseline.

9.3.1 Extent of Exposure

Study drug exposure (Number of doses) will be summarized using the eight-point descriptive summary by study periods. The source for exposure data is the drug accountability data domain.

Study drug compliance will be assessed using the following categories using the same source as the drug exposure data by study periods:

- 100%;
- 95%;
- 90%;
- 80%;
- <80%.

Compliance will be calculated overall (months 1-12), months 9-12, months 6-9, months 3-6 and months 1-3.

Study drug administration (date/time and study day) will be provided in a data listing. The source for study drug administration is the diary data domain.

9.3.2 Adverse Events

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will present by system organ class (SOC), preferred term (PT) and severity and/or relatedness, the frequency and percentage of subjects reporting each observed event.

A treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from TEAEs. Treatment-limiting AEs are defined as any event that leads to permanent or temporary discontinuation from treatment, or a reduction in the treatment dose.

Summary of adverse events will be dependent on adverse events observed. If no adverse events meeting a specific table are observed, the summary table will not be completed. Blank summary tables will not be utilized. The following is the list of adverse event tables:

Overall:

- Overall Summary of Adverse Events

By preferred term:

- Treatment-emergent Adverse Events by SOC and PT
- Treatment-emergent Adverse Events by PT
- Treatment-emergent Adverse Events by SOC and PT occurring in more than 1% of Study population
- Treatment-emergent Adverse Events by SOC, PT and LABA Use

By severity:

- Treatment-emergent Adverse Events by SOC, PT and Severity
- Moderate or Severe Treatment-emergent Adverse Events by SOC and PT
- Serious Adverse Events
- Deaths during Study

By relatedness:

- Drug-Related Treatment-emergent Adverse Events by SOC and PT
- Drug-Related Treatment-emergent Adverse Events by SOC, PT and LABA Use
- Drug-Related Treatment-emergent Adverse Events by SOC, PT and Severity
- Moderate or Severe Drug-Related Treatment-emergent Adverse Events by SOC and PT
- Drug-related Serious Adverse Events

Other:

- Adverse Events Leading to Premature Study Drug Discontinuation
- Adverse Events Leading to Temporary Interruption of Study Drug

The overall summary of adverse events will include the following summary lines, any AE, moderate or severe AEs, moderate or severe AEs related to Study Drug, serious AEs, serious AEs related to Study Drug, AEs leading to discontinuation, AEs leading to interruption, deaths during Study.

9.3.2.1 Exacerbations

Exacerbations will be summarized using both exacerbations reported as adverse events [redacted]

[redacted]

Exacerbations Reported as Adverse Events

A summary of COPD exacerbations, as defined in the protocol, and reported with an AE PT of COPD will be summarized descriptively by severity. Exacerbation data will be summarized for the following categories using counts and percentages: a) All exacerbations, b) Moderate or severe exacerbations, and c) Severe exacerbations.

In addition, a negative binomial model will be fit to assess the exacerbation rate per year and relative risk using the same categories.

[redacted]

In addition, time to first exacerbation will be summarized using Kaplan-Meier methodology.

[redacted]

9.3.2.2 Cardiovascular Events of Interest

Adjudication Summary of Treatment-Emergent Cardiovascular Adverse Events by Cardiovascular Category will summarize, by CEC class categories, adjudicated events:

- All-cause Death
- Cardiovascular death
- Non-cardiovascular death
- Myocardial infarction/Unstable Angina
- Stroke/TIA
- Heart Failure
- Cardiac Arrhythmia
- Atrial arrhythmia
- Ventricular arrhythmia

[redacted]

9.3.2.3 Antimuscarinic Adverse Events

Antimuscarinic TEAEs are of interest as a common event in the drug class and will be summarized by preferred terms. The preferred terms for TEAEs considered antimuscarinic are as follows:

- Constipation
- Dry mouth
- Dysuria
- Worsening of urinary retention
- Worsening of narrow-angle glaucoma.

9.3.3 Vital Signs

For each nominal time point, vital signs will be summarized in terms of observed values and changes from Baseline. Vital signs outliers will be flagged in the listing.

Table 10: Vital Signs Outlier Thresholds

Heart Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
<40 >110	<85 >160	<45 >100

9.3.4 ECG

A summary of ECG parameters, parameters reported separately QTcF, PR interval, QT interval, QRS duration, RR, and HR, will be summarized in terms of observed values and change from baseline.

Subjects without post-baseline measurement for a given treatment period will be excluded from the summary statistic (e.g., denominator of the summary statistic) for that time point.

All recorded values by central reader at ECG core lab for the standard 12-lead electrocardiogram parameters will be presented in a by-subject listing.

Outlier Analysis

The number of subjects with absolute ECG values and change from baseline in the ranges shown in Table 11 will be presented in Electrocardiogram Outlier Summary by Visit and Time Point.

In addition in the same summary, QTcF will also be summarized by the following categories, Normal (males <430, females ≤450), Borderline (males (>430, ≤450); females (>450, ≤470)) and Prolonged (males >450, females >470).

Individual ECG data collected during the study will be presented in a listing. A separate listing of subjects with values of QTcF >500 msec or an increase >60 msec will be provided, as necessary.

Figures

Cumulative distribution plots will be provided for maximum change in QTcF by day.

Investigator Assessment of ECG Readings

The investigators' assessment of ECGs as normal, abnormal and clinically significant, or abnormal but not clinically significant will be summarized for baseline and for each visit.

Table 11: ECG Test Outlier Thresholds

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percentage Change From Baseline (%)	QRS Interval (msec)	QT_cF (msec)	QT_cF change from Baseline (msec)
>120	>20	>200	>15	>120	Males:	≤30
>130	>30	>220	>25		≤430	>30, ≤60
					>430	>60
					>450	
					>470	
					>480	
					>500	
					Females:	
					≤450	
					>450	
					>470	
					>480	
					>500	

9.3.5 Holter ECGs

Descriptive statistics will be provided to the results of Holter interpretation which will include the following heart rate (HR) variables:

- Maximum (max), minimum (min) and mean HR, for the entire recording,
- Supraventricular premature beats (PACs) singles and couplets,
- Ventricular premature beats (VPCs) singles and couplets normalized for 24 hours,

Subjects without post-baseline measurement for a given treatment period will be excluded from the summary statistic (e.g., denominator of the summary statistic) for that time point.

All the Holter ECG variables will be presented in a by-subject listing.

The detailed analysis plan for Holter's ECG data will be detailed in a separate document.

9.3.6 Clinical Laboratory Results

Laboratory data, hematology, serum chemistry and urinalysis, will be summarized in terms of observed values, changes from baseline for each period. In addition, changes from baseline for each period relative to normal ranges (e.g., shifts from normal to abnormal high/low) will be summarized in hematology: shift from baseline, serum chemistry: shift from baseline and urinalysis: shift from baseline.

Listings will flag laboratory values that are outside of normal range.

Listings of all abnormal lab values for each of the Laboratory sets will be provided.

9.3.7 Medical History

Medical history collected at screening will be provided in a data listing and a summary table.

9.3.8 Prior and Concomitant Medications

Prior and concomitant Medications will be listed and summarized separately. Tables and listings will be provided for concomitant bronchodilators, concomitant corticosteroids, Concomitant NON-COPD medications, Post-treatment Bronchodilators. Coding logic for each group is in Appendix 3.

9.3.9 12-month Vital Status

All subjects were followed for vital status at 12-months. Subjects who discontinued were contacted around their expected Day 365 visit to collect vital status. A Vital Status Summary will estimate the probability of being alive at 12-months using a Kaplan-Meier estimate to account for subjects who were lost to follow-up.

9.4 Exploratory Efficacy Analyses

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9.4.9 Exploratory Efficacy Evaluation: [redacted]

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9.4.10 Exploratory Efficacy Evaluation: [redacted]

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9.4.12 Multiplicity Adjustment

No multiplicity adjustment of p-values for the efficacy endpoints will be made.

Appendix 1: Reporting Structures for Data Summary

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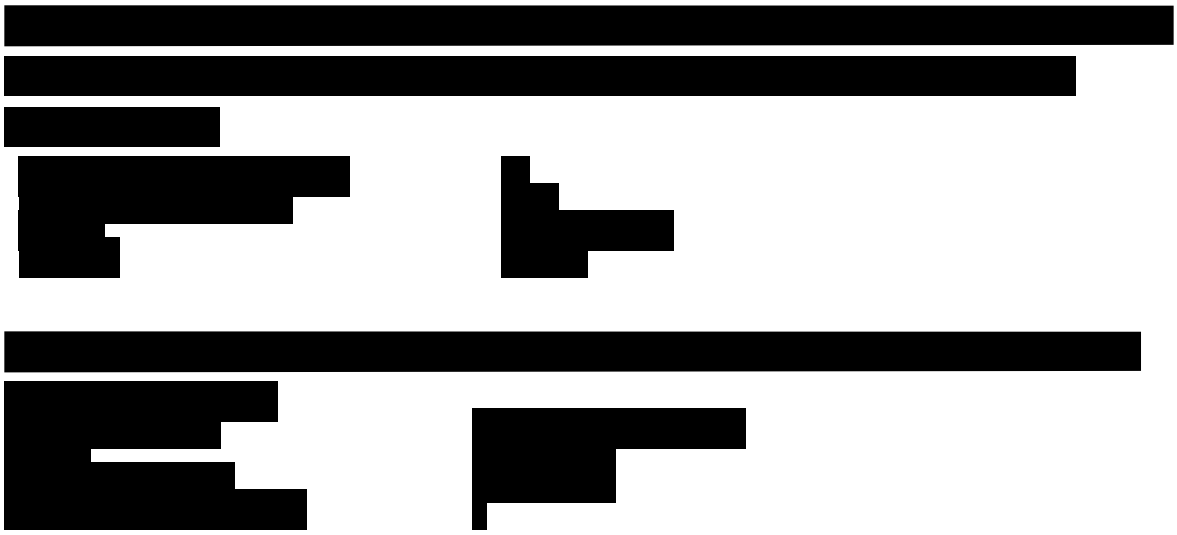

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Appendix 3: Coding Logic for Concomittant Medications and Adverse Events of Interest

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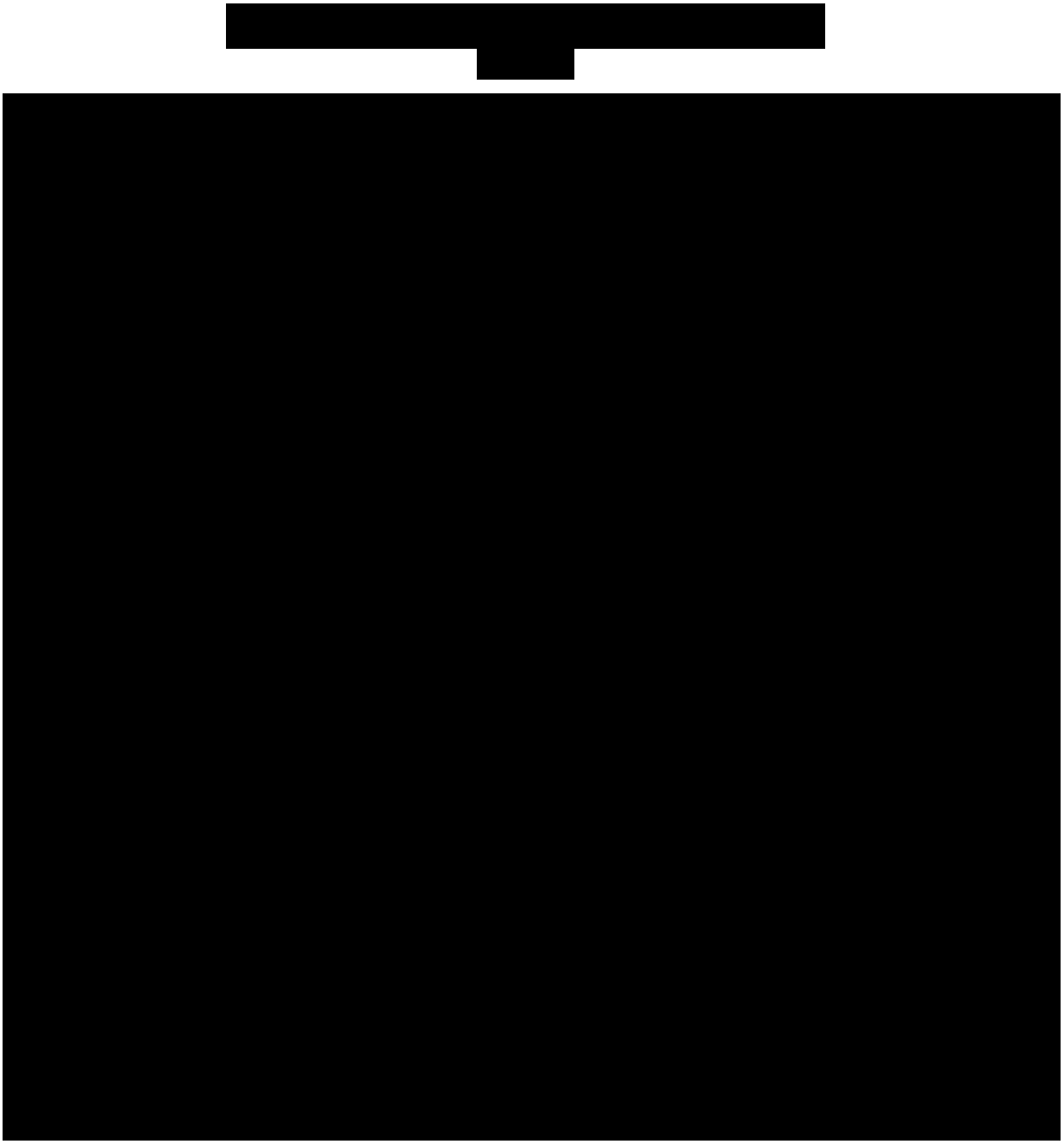

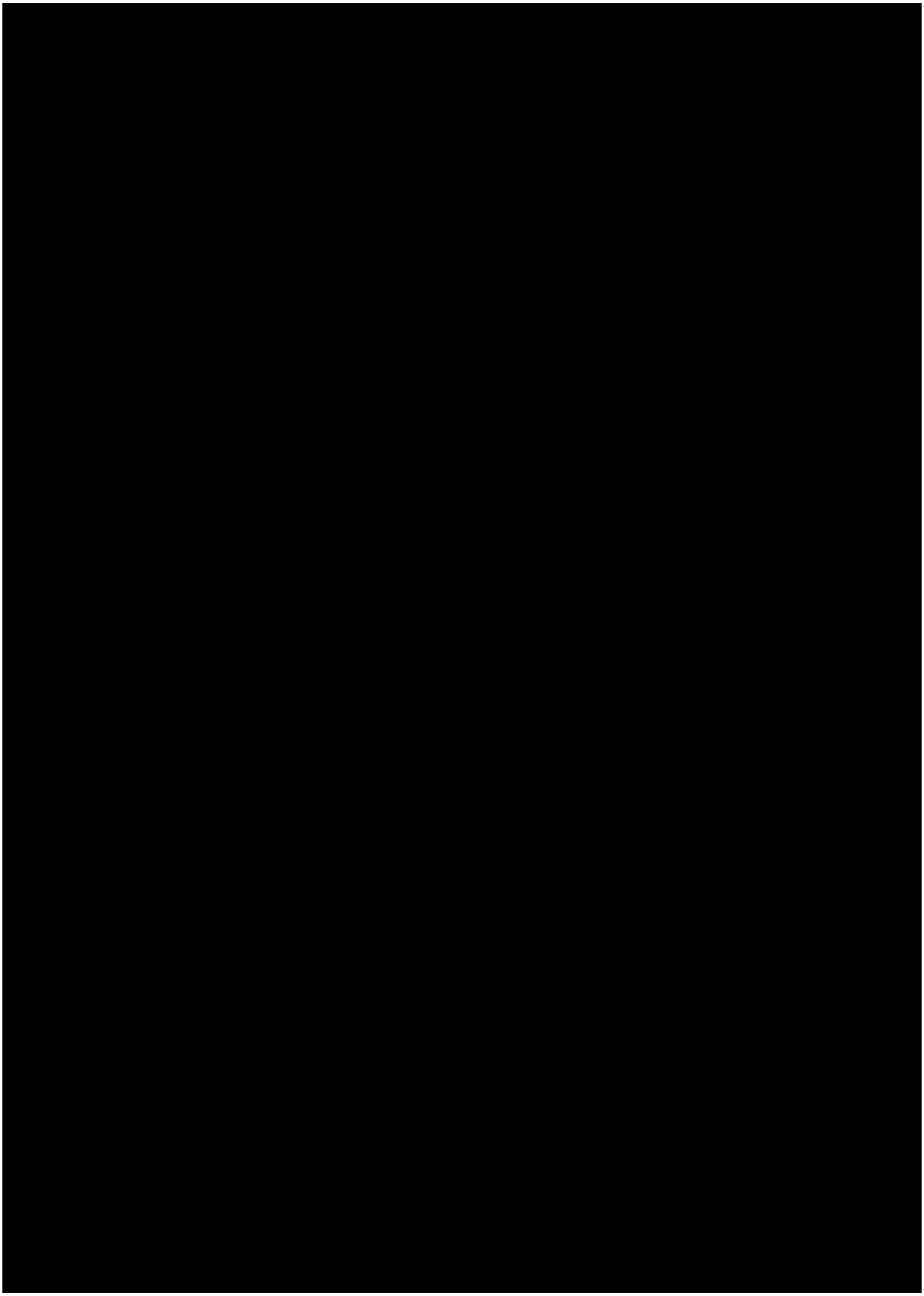

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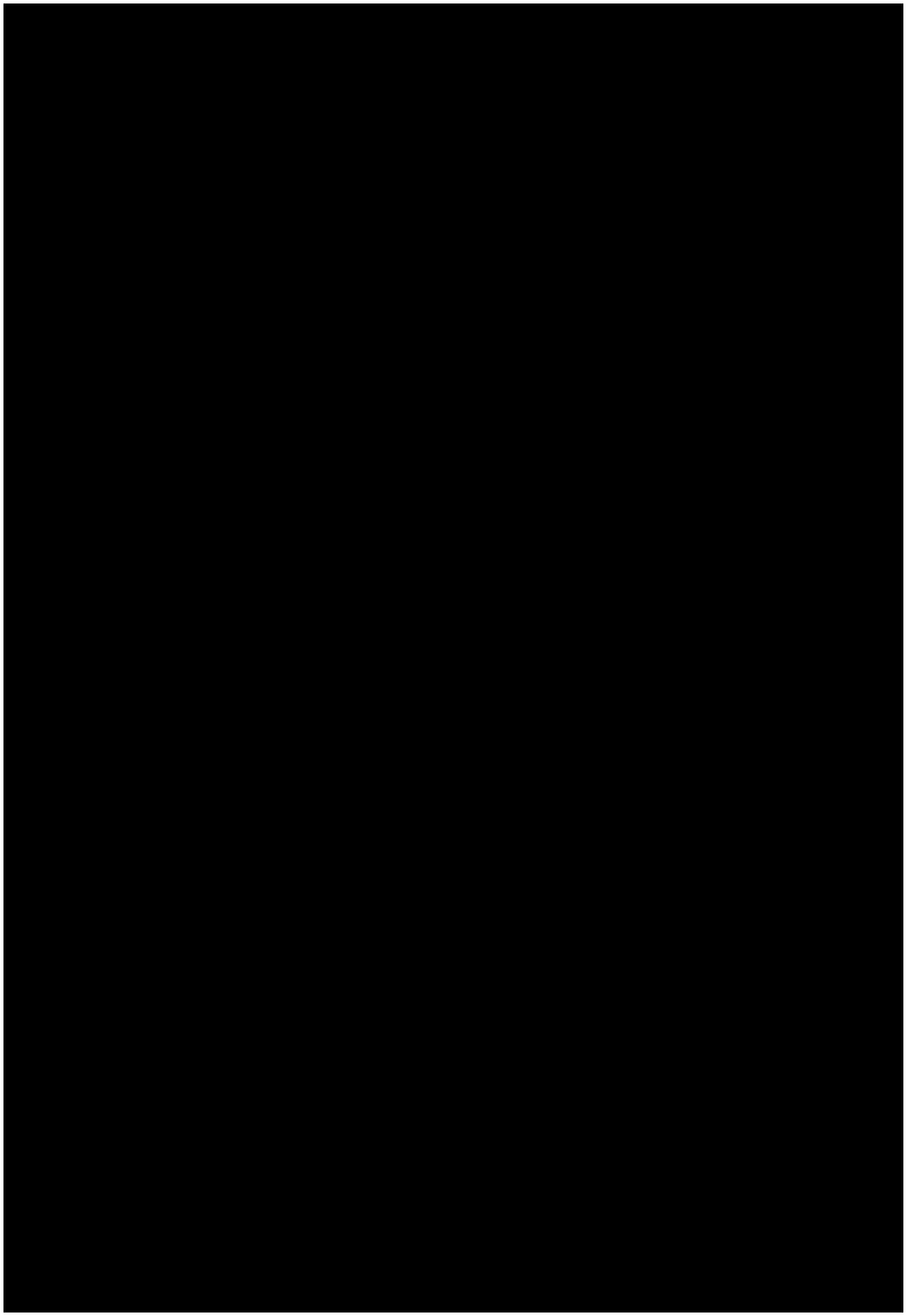

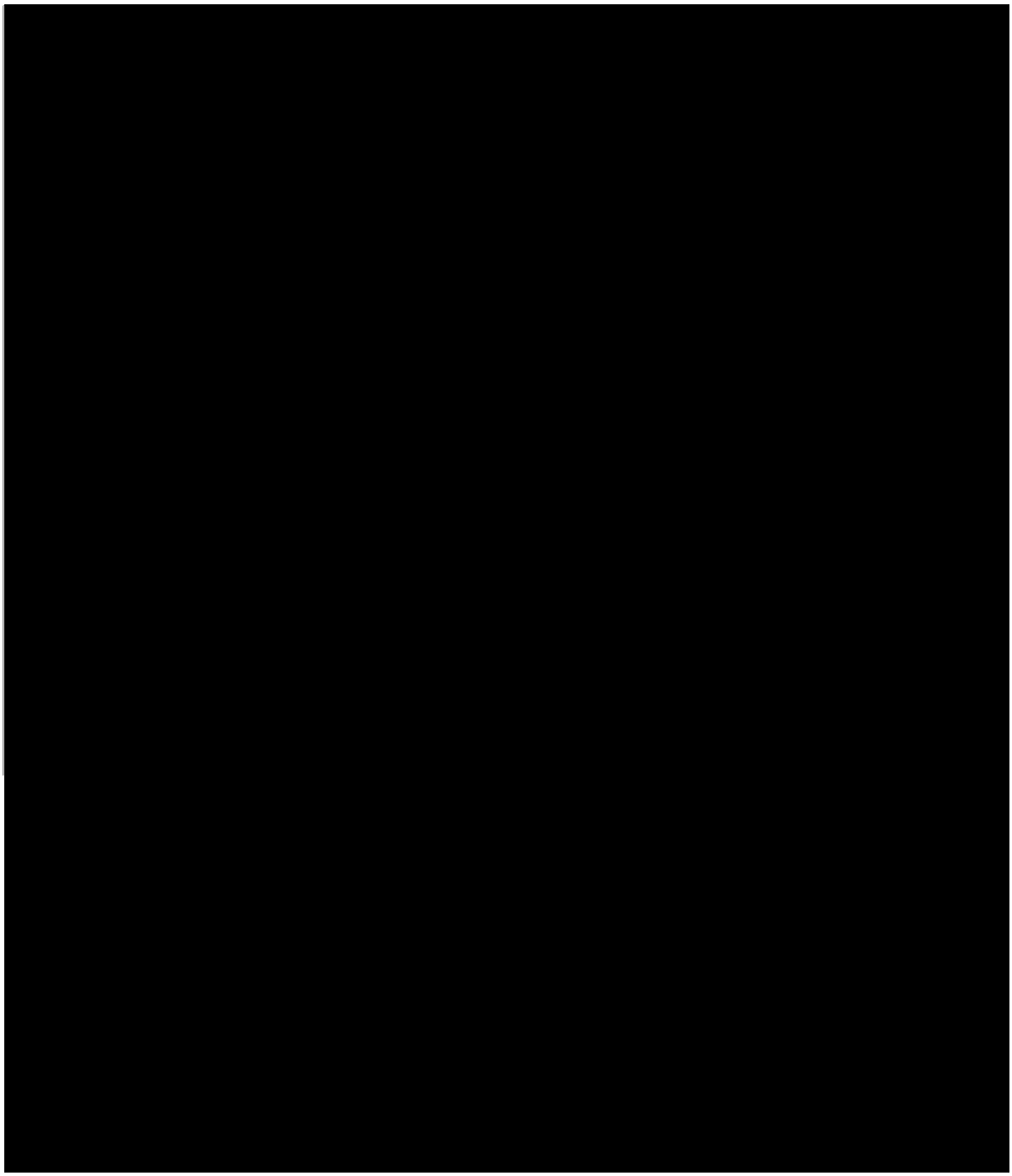

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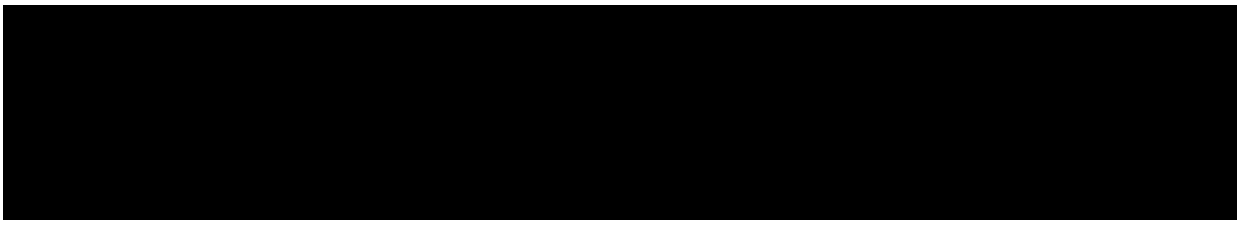

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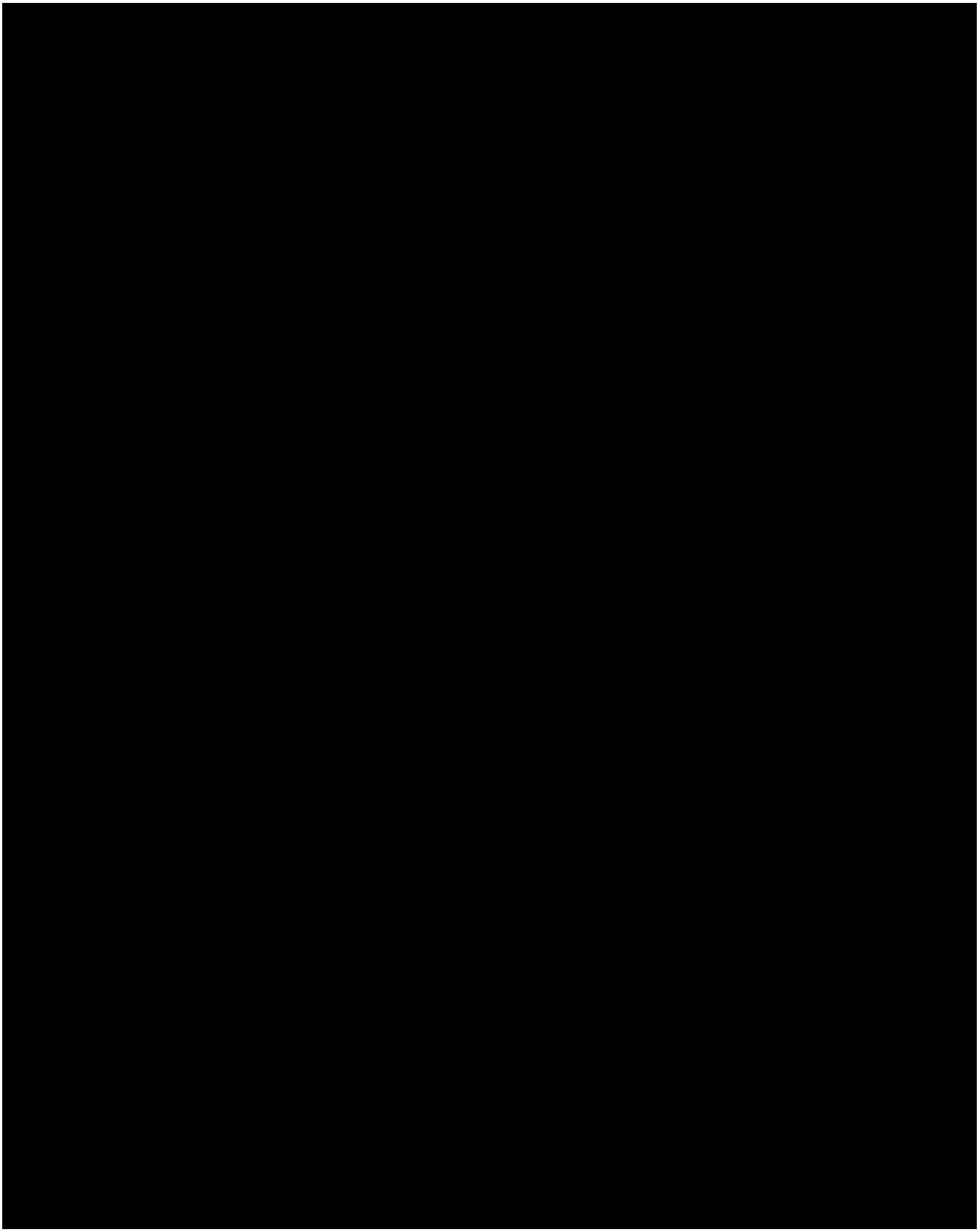

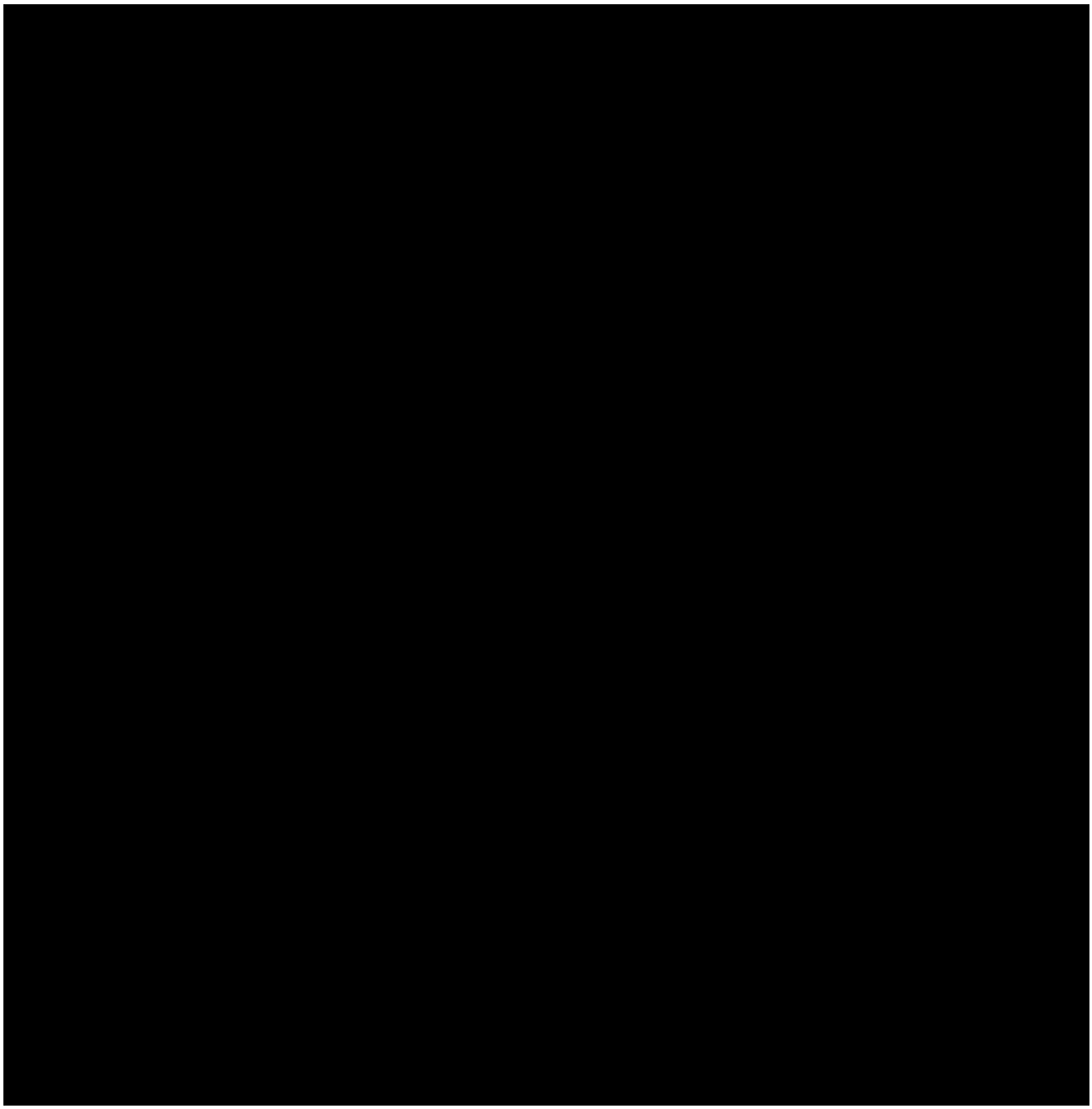

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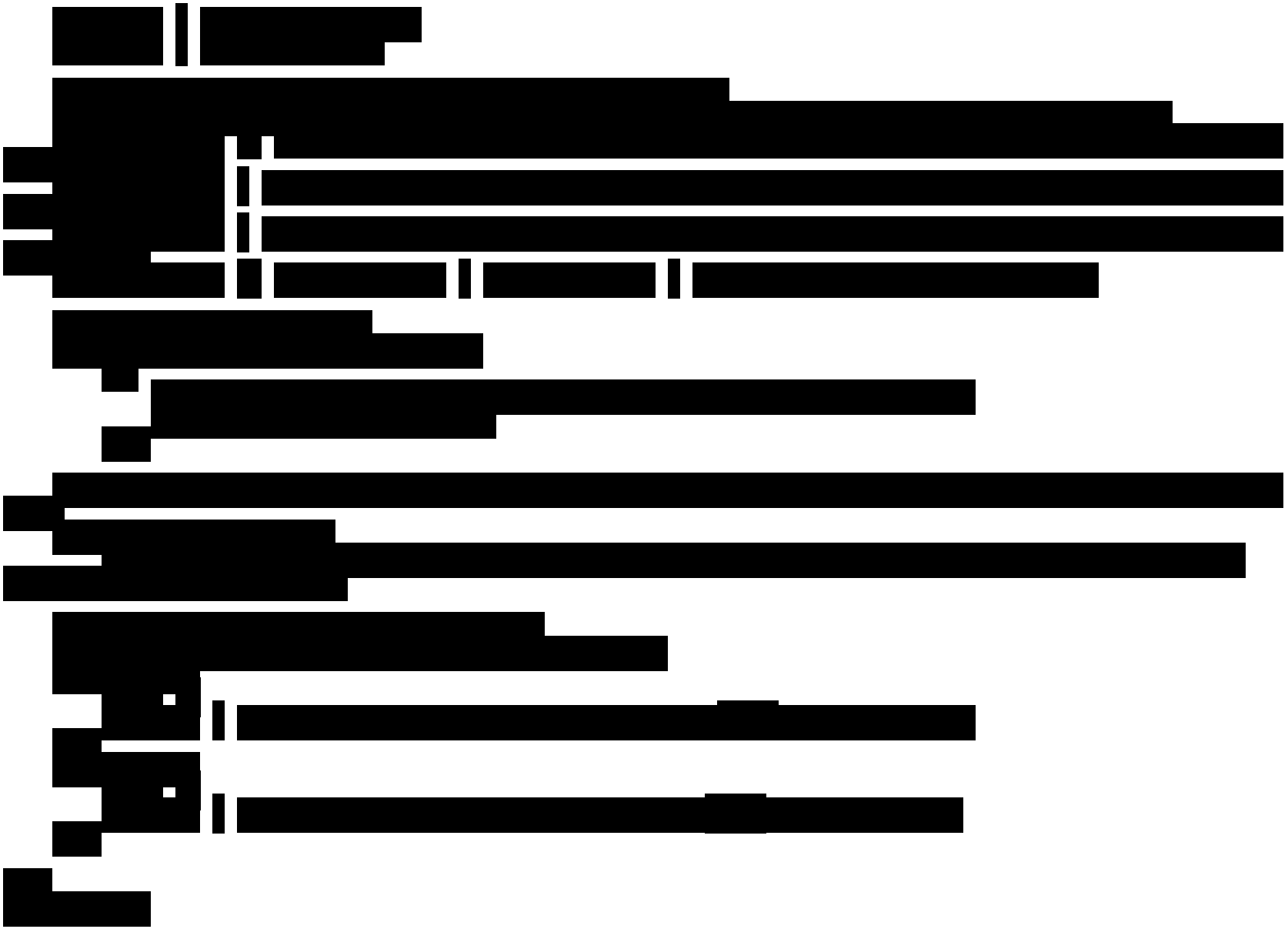
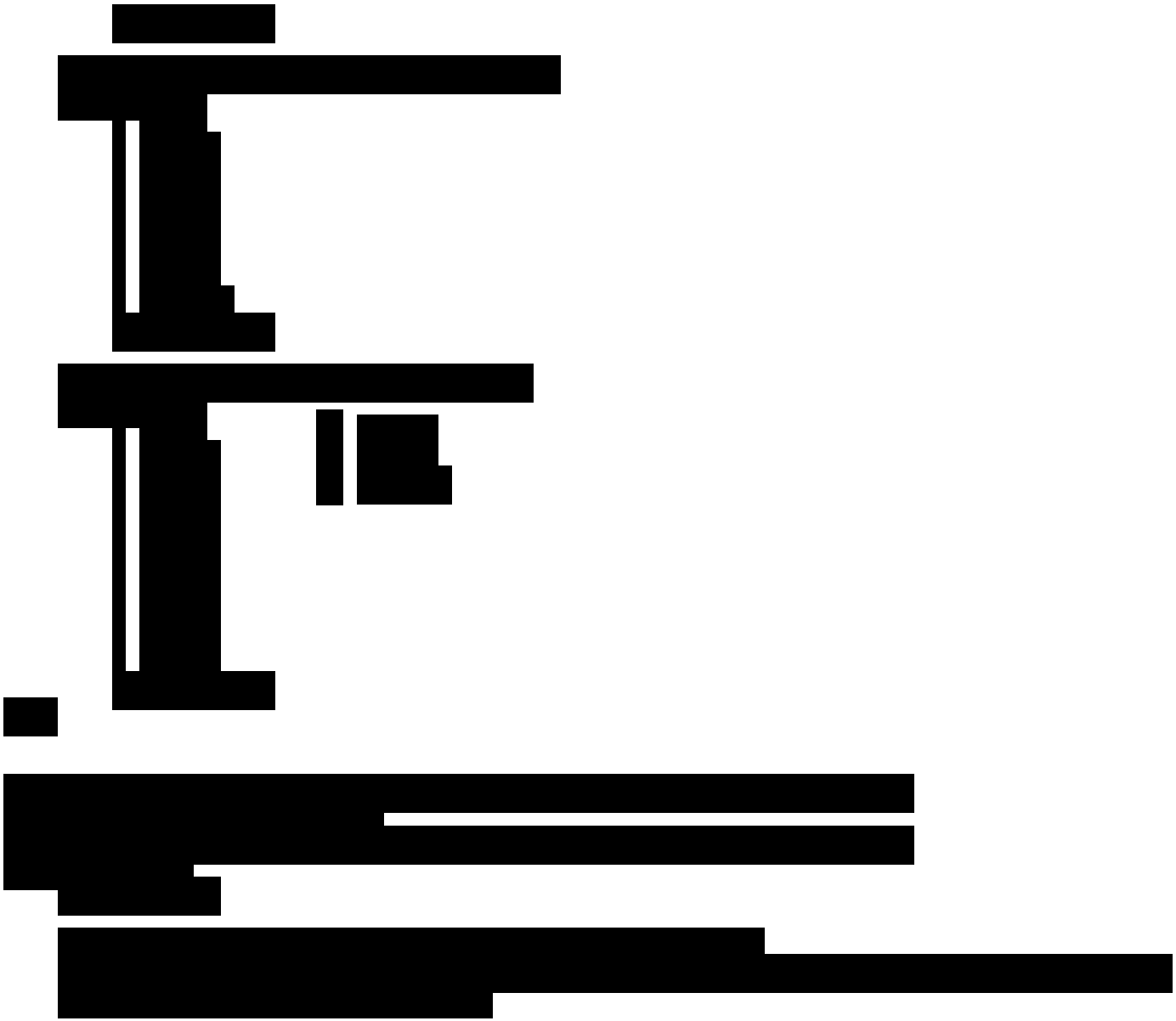
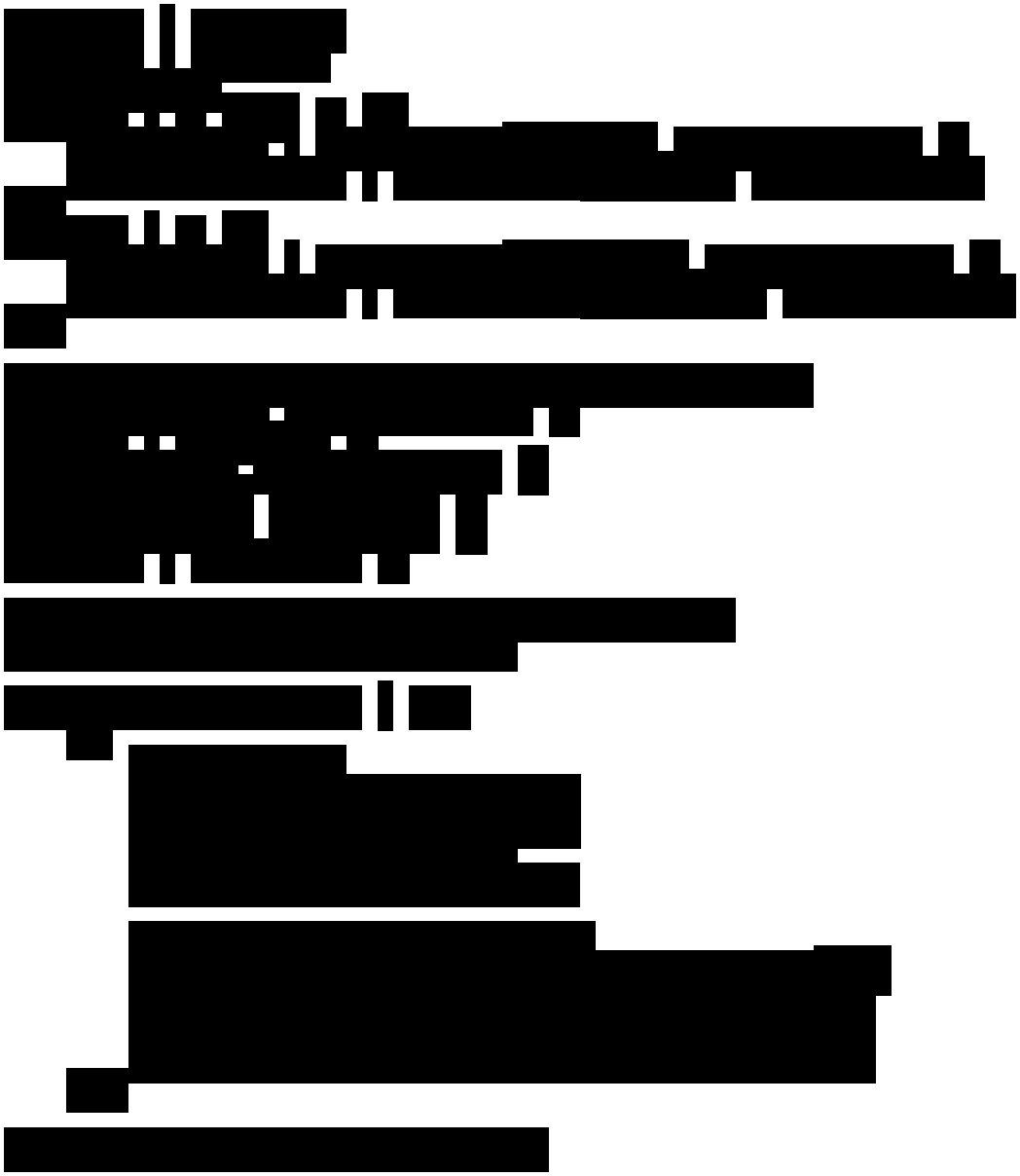
Appendix 14: SAS Macros







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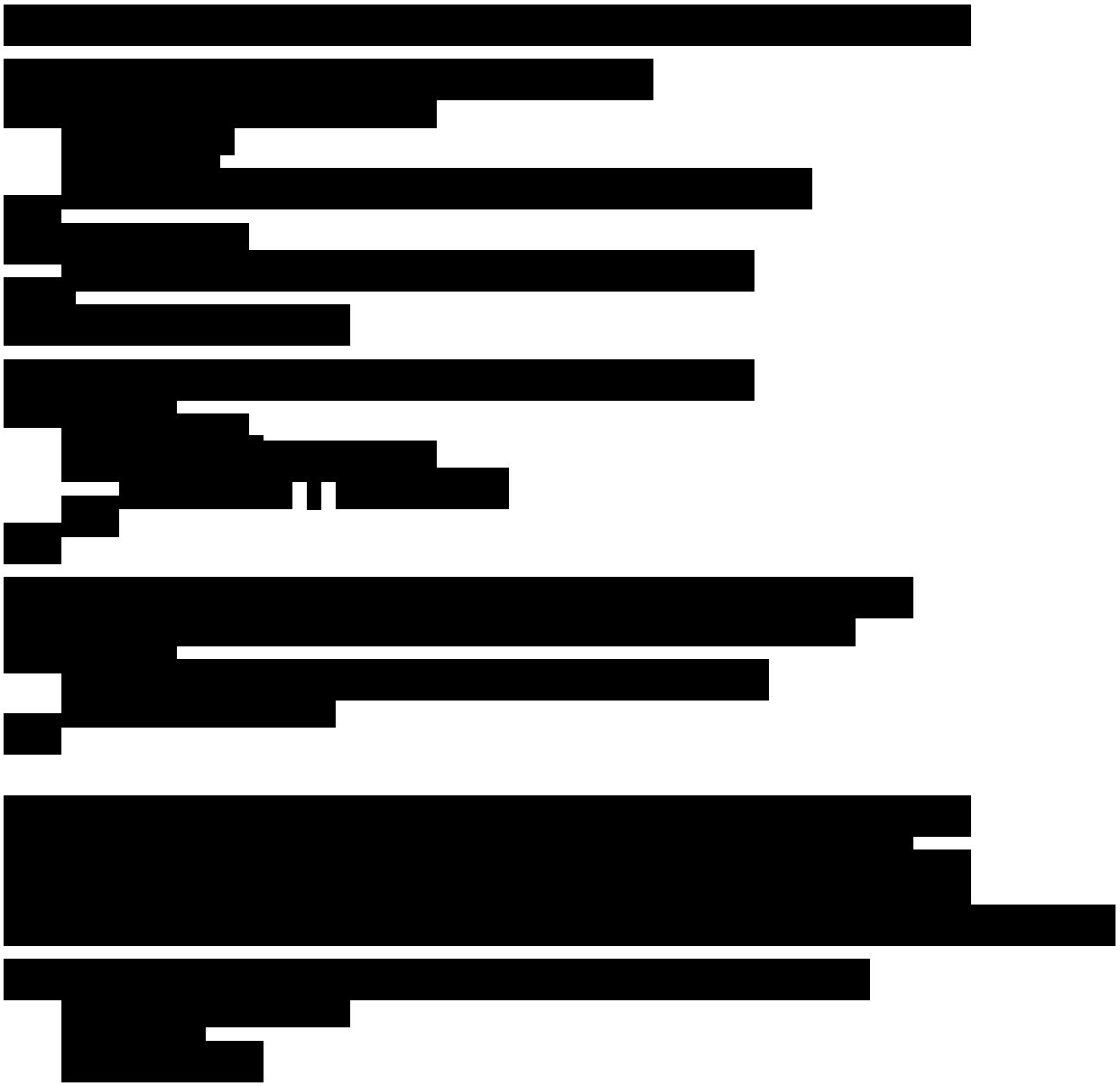

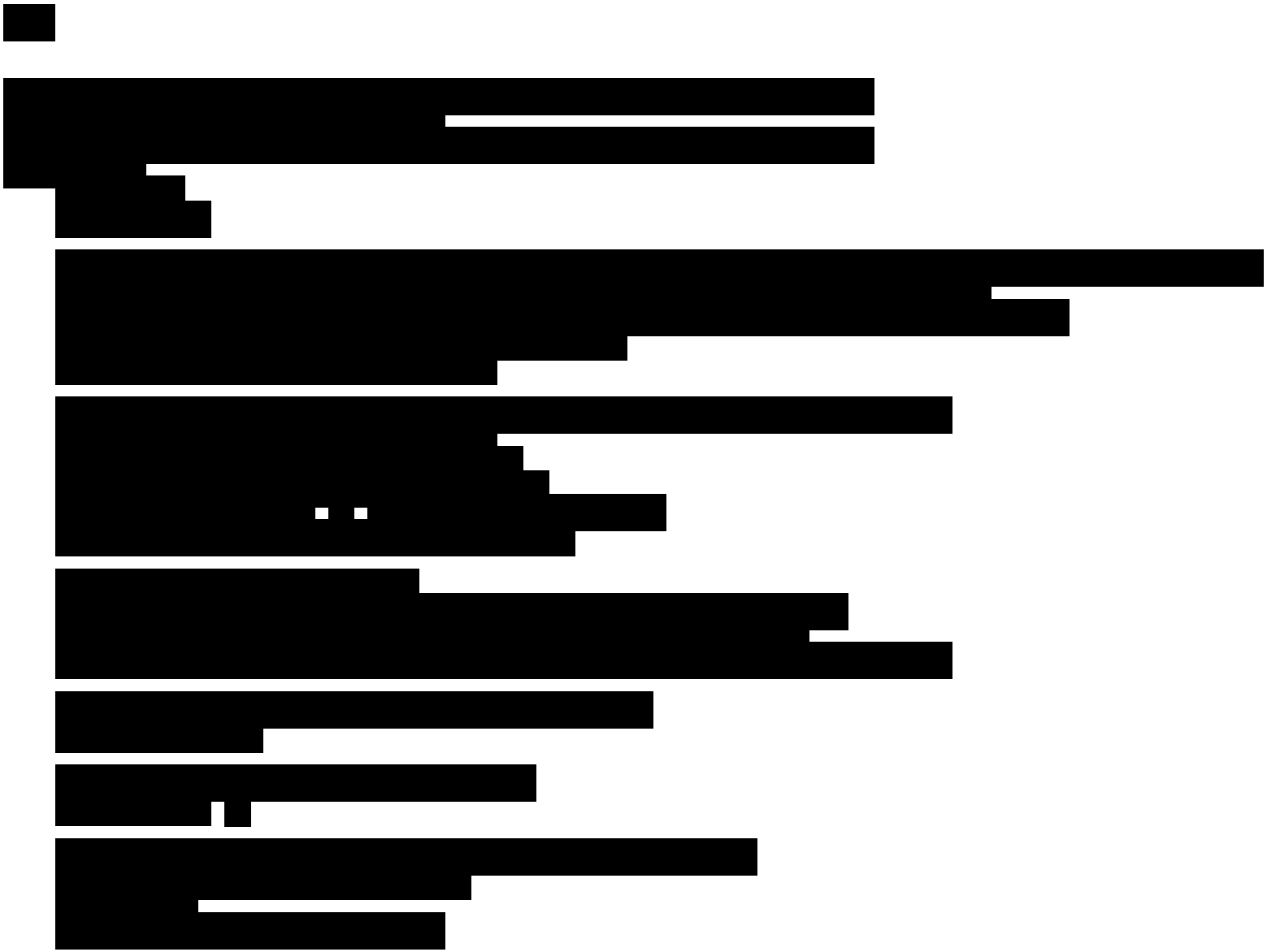

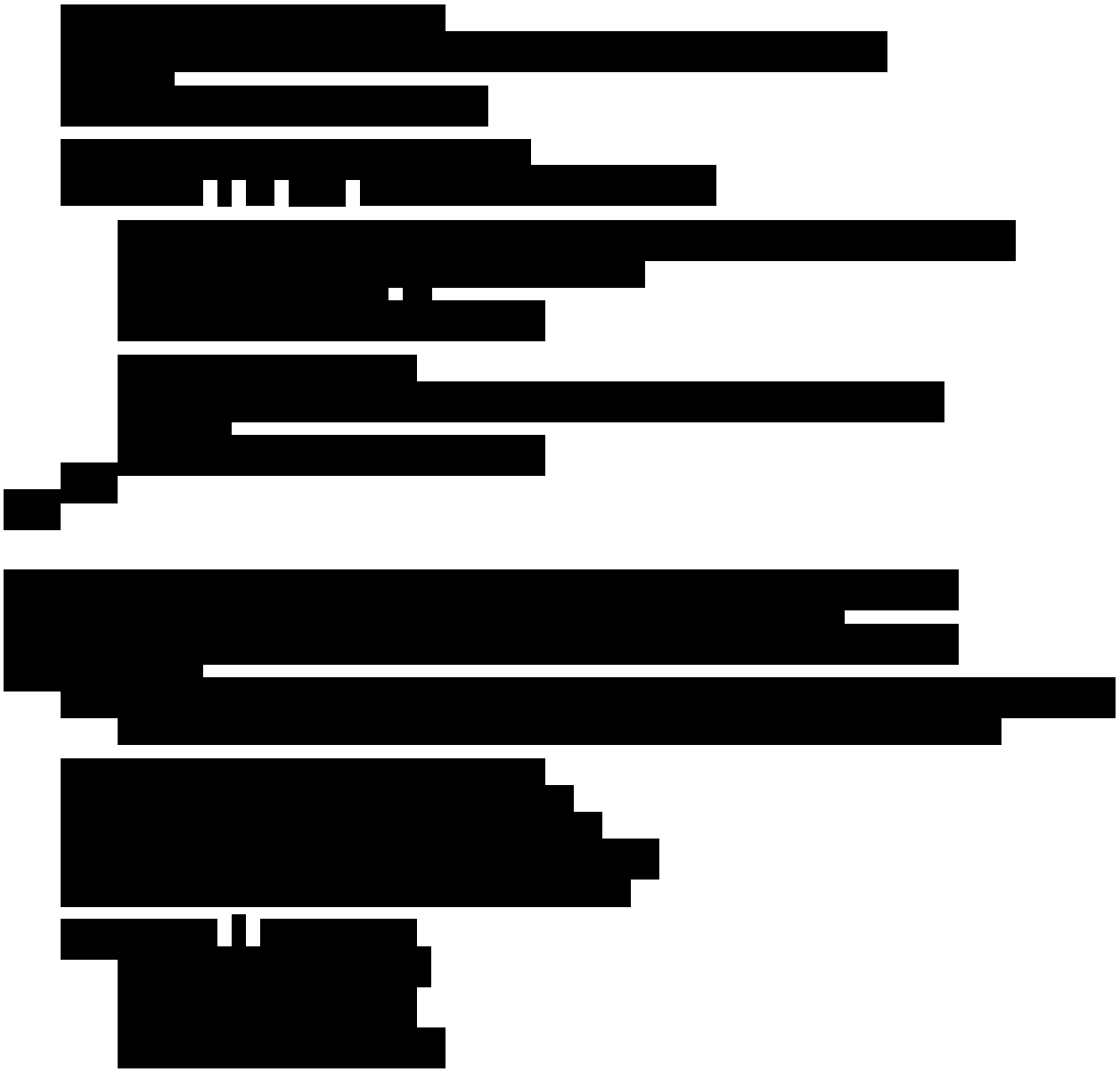

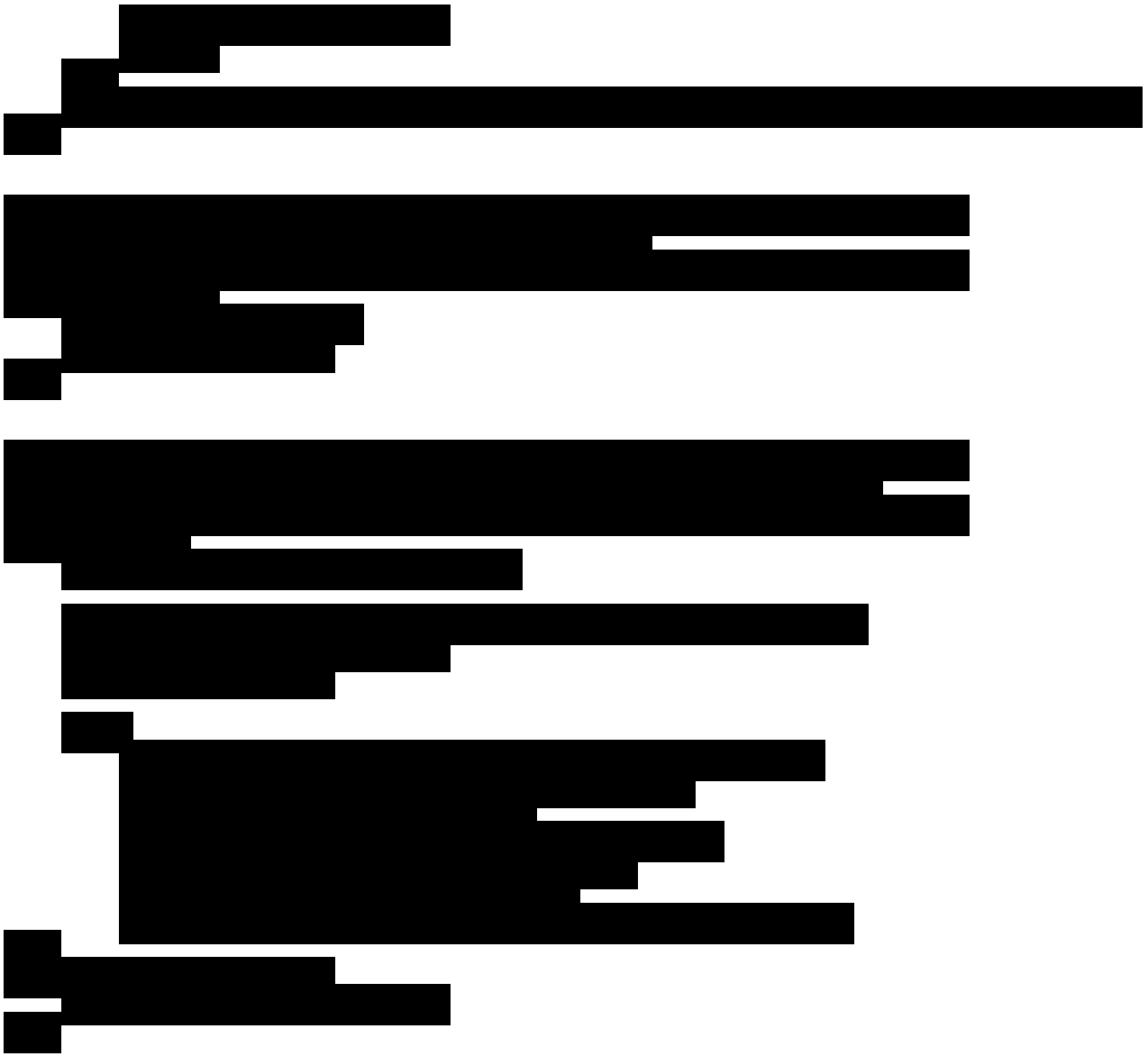

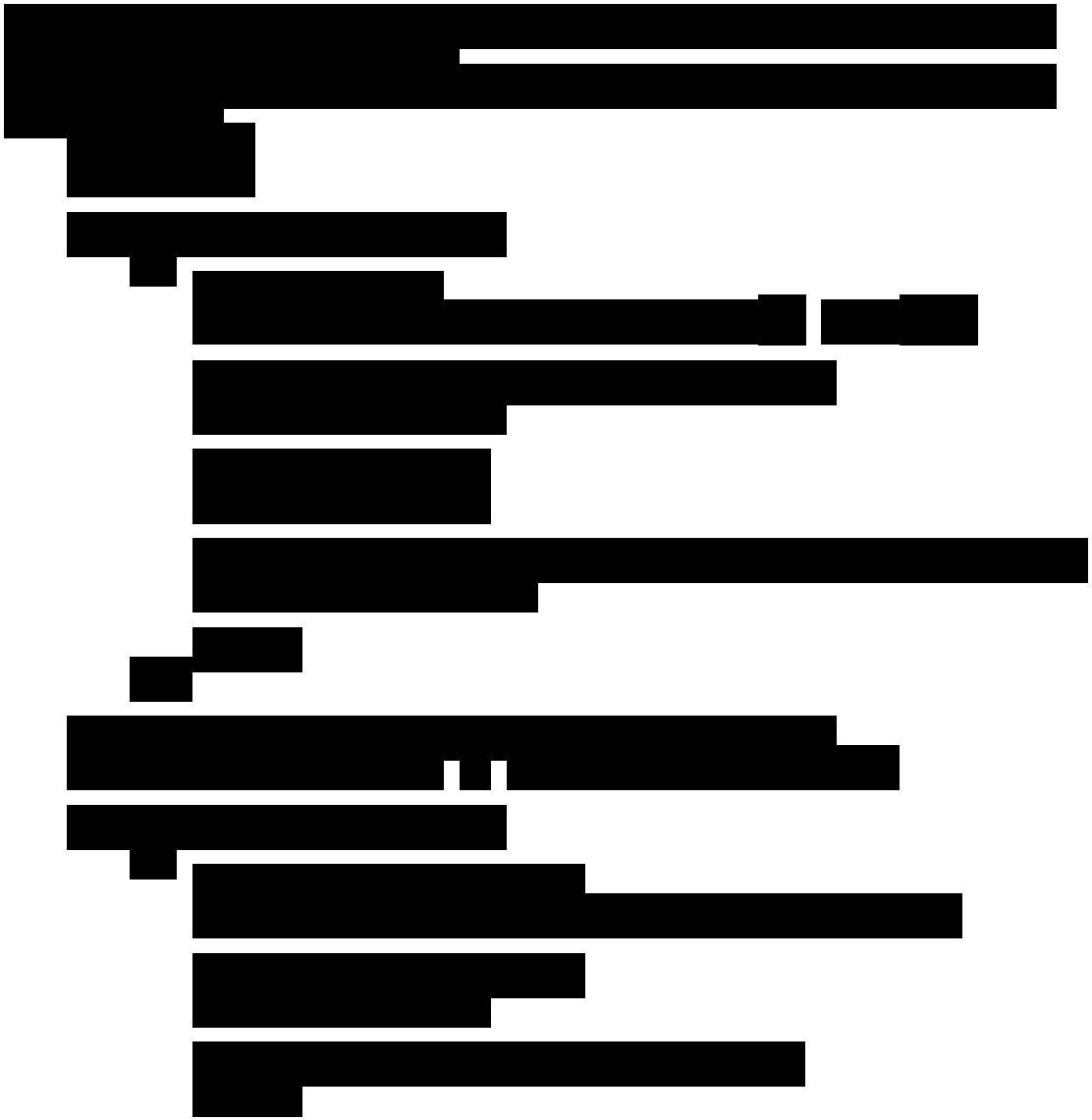

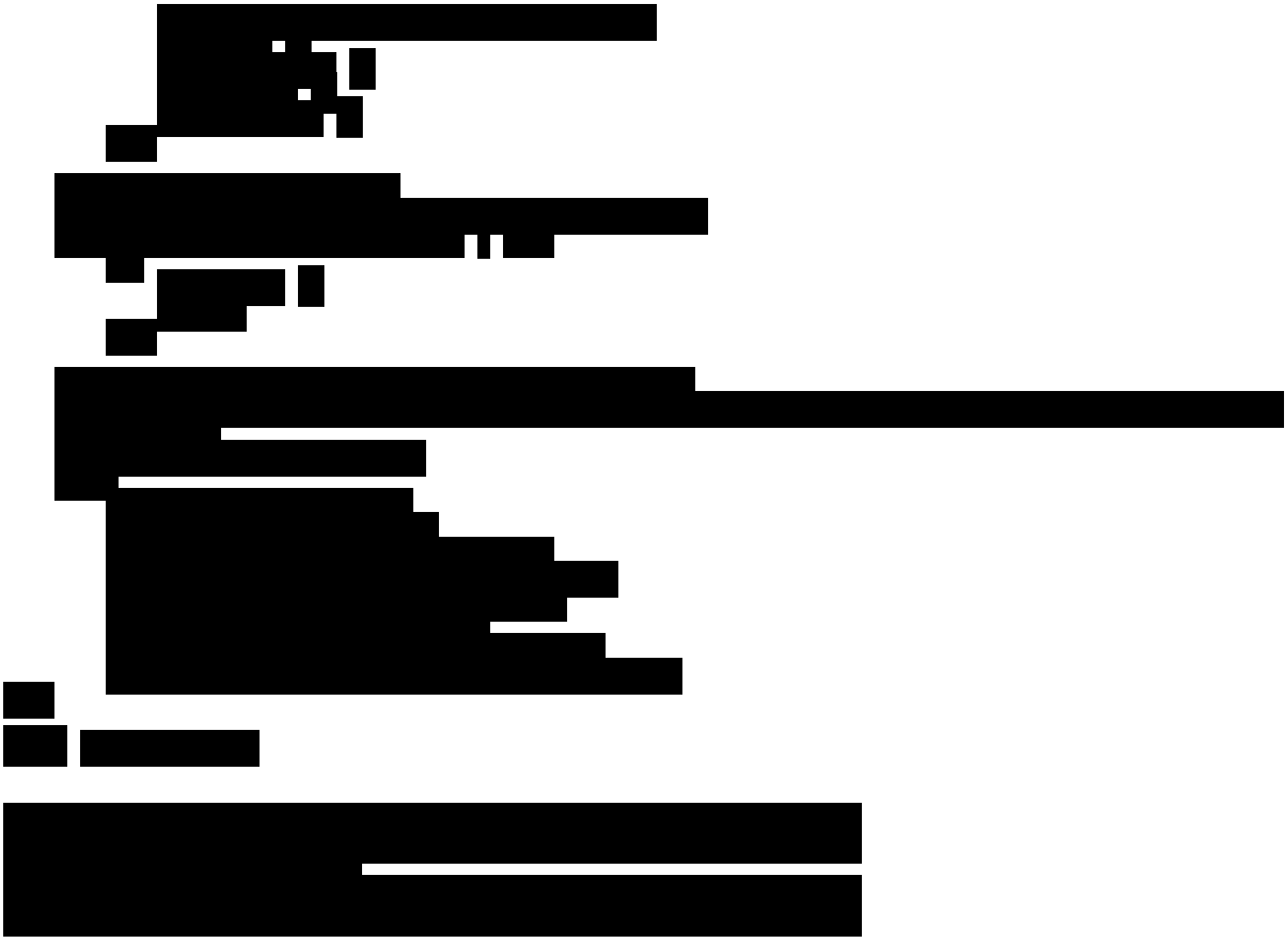

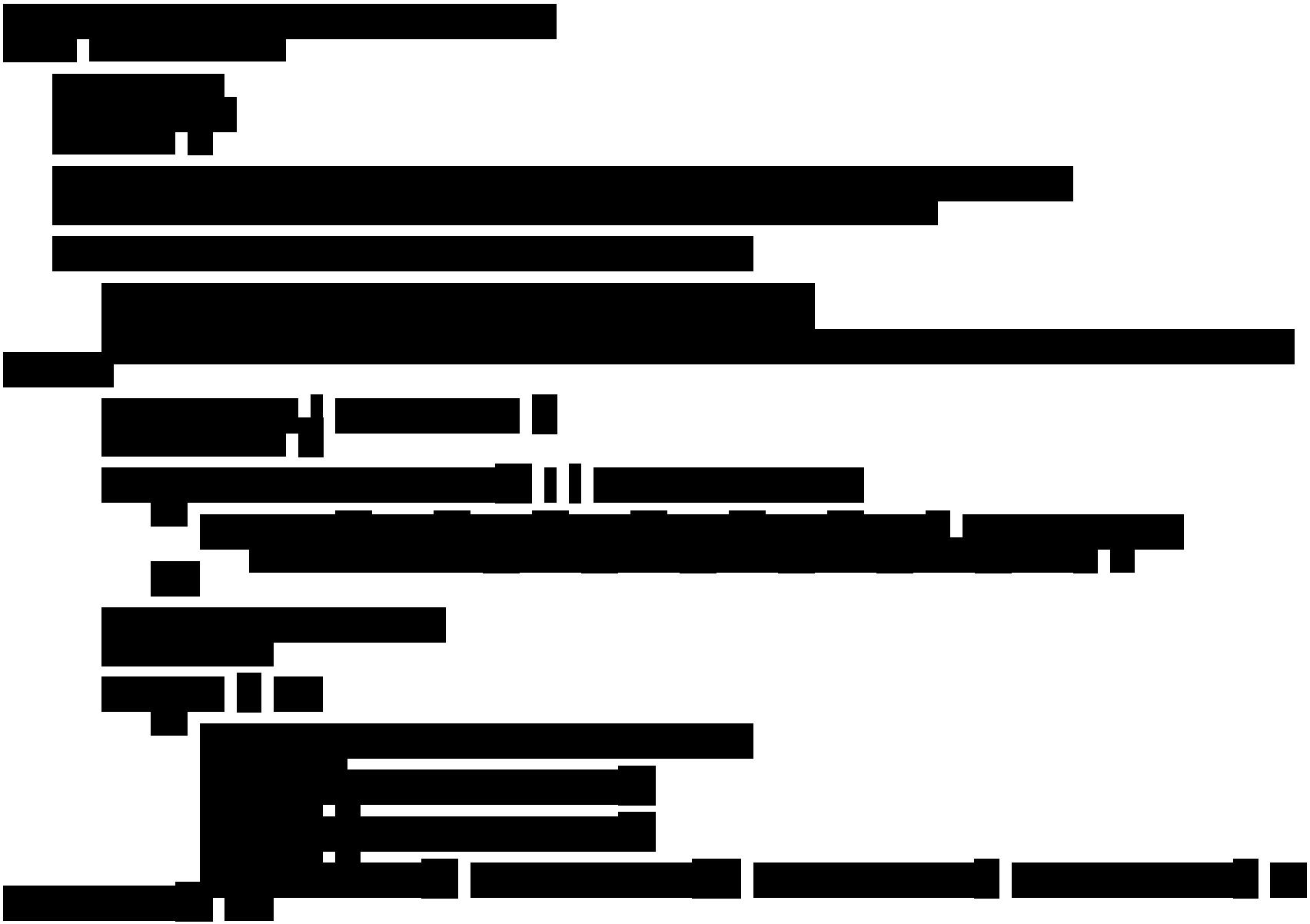

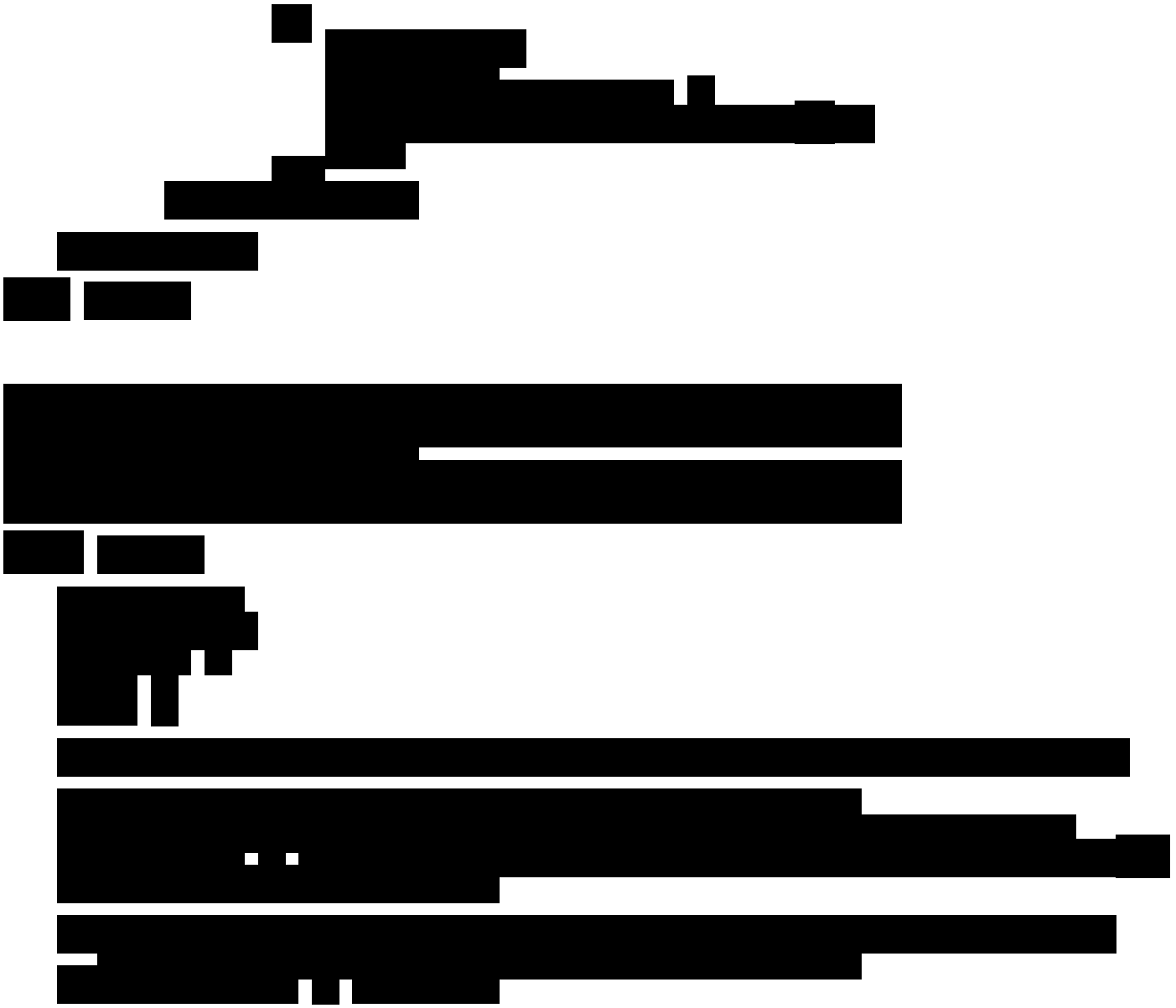

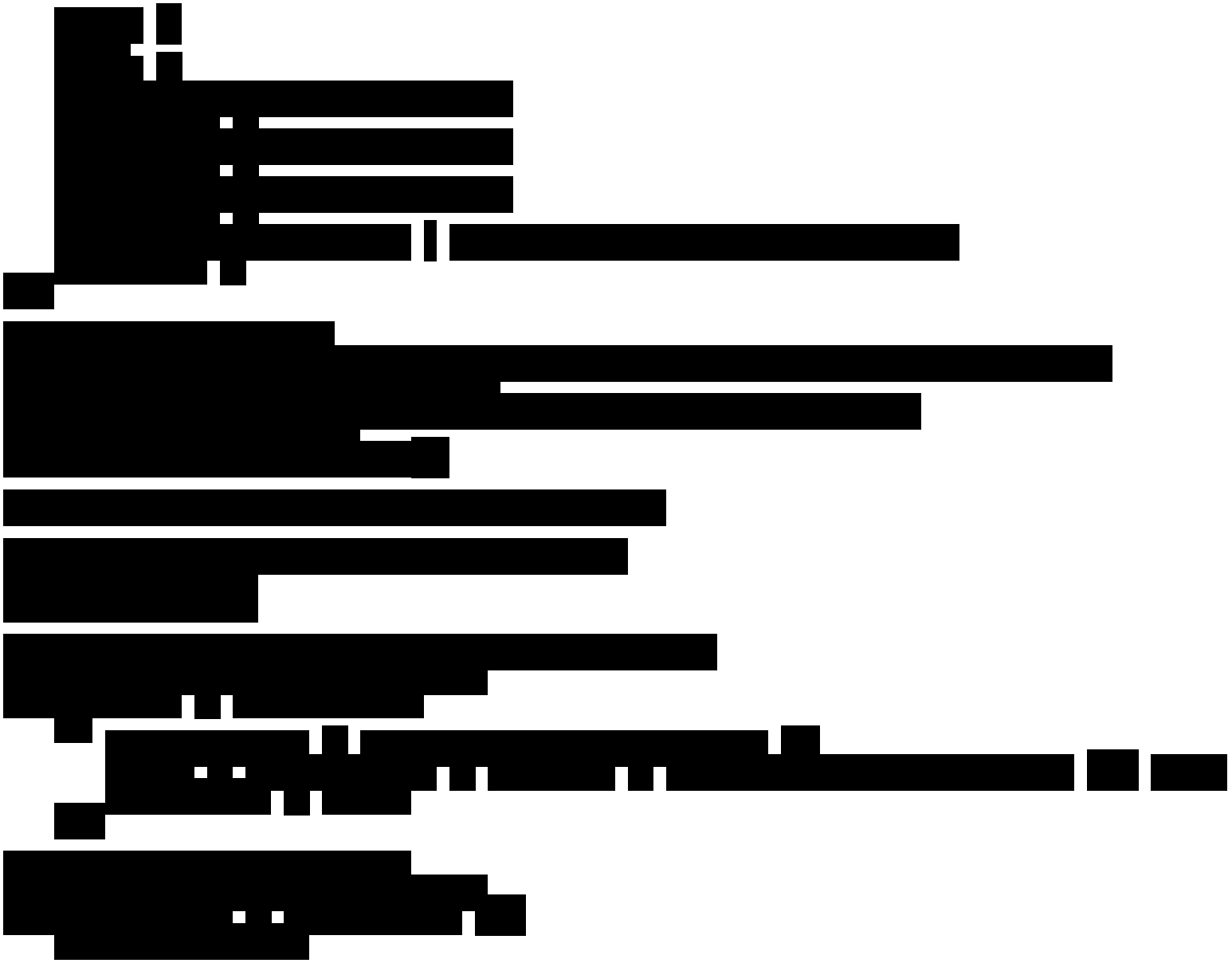

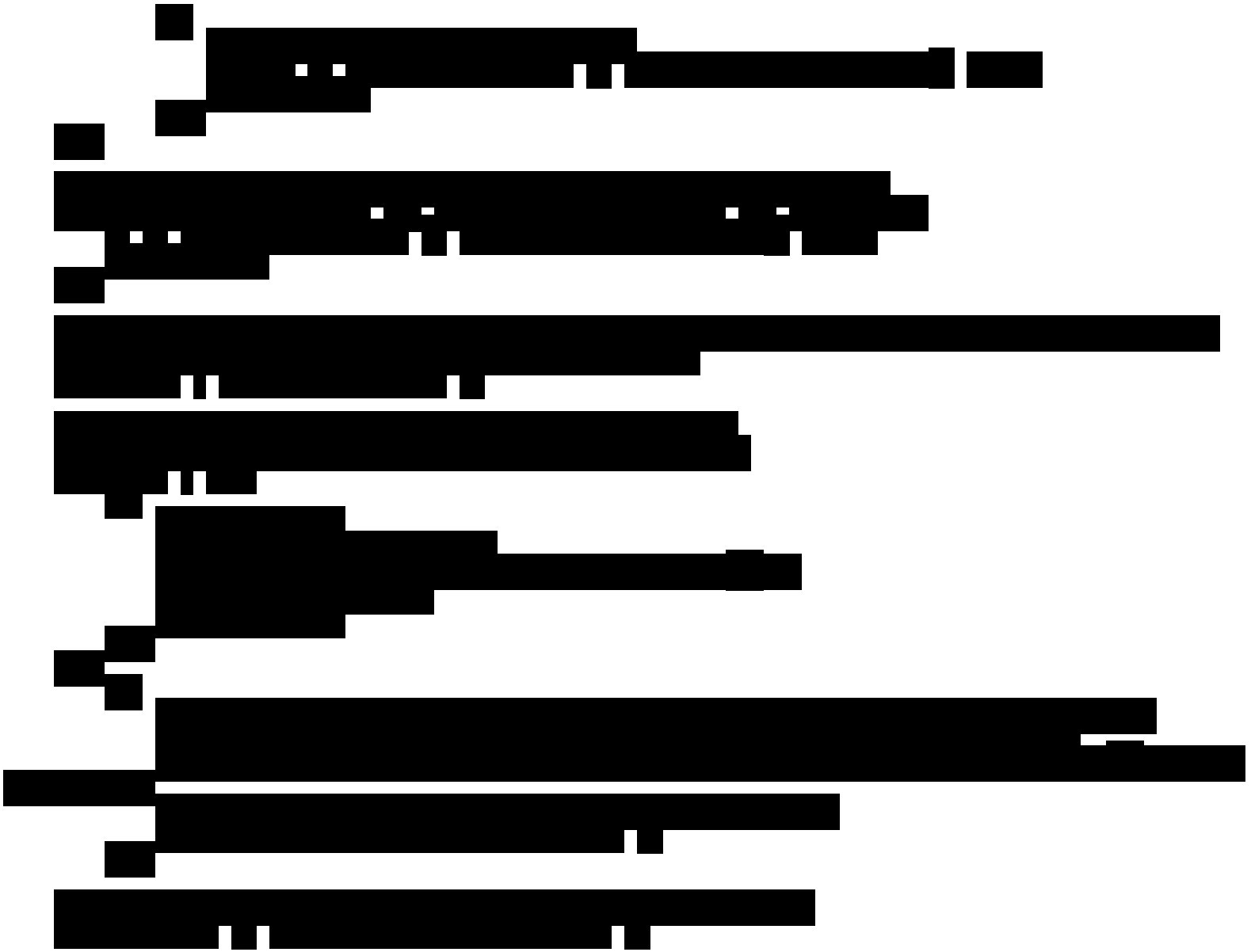

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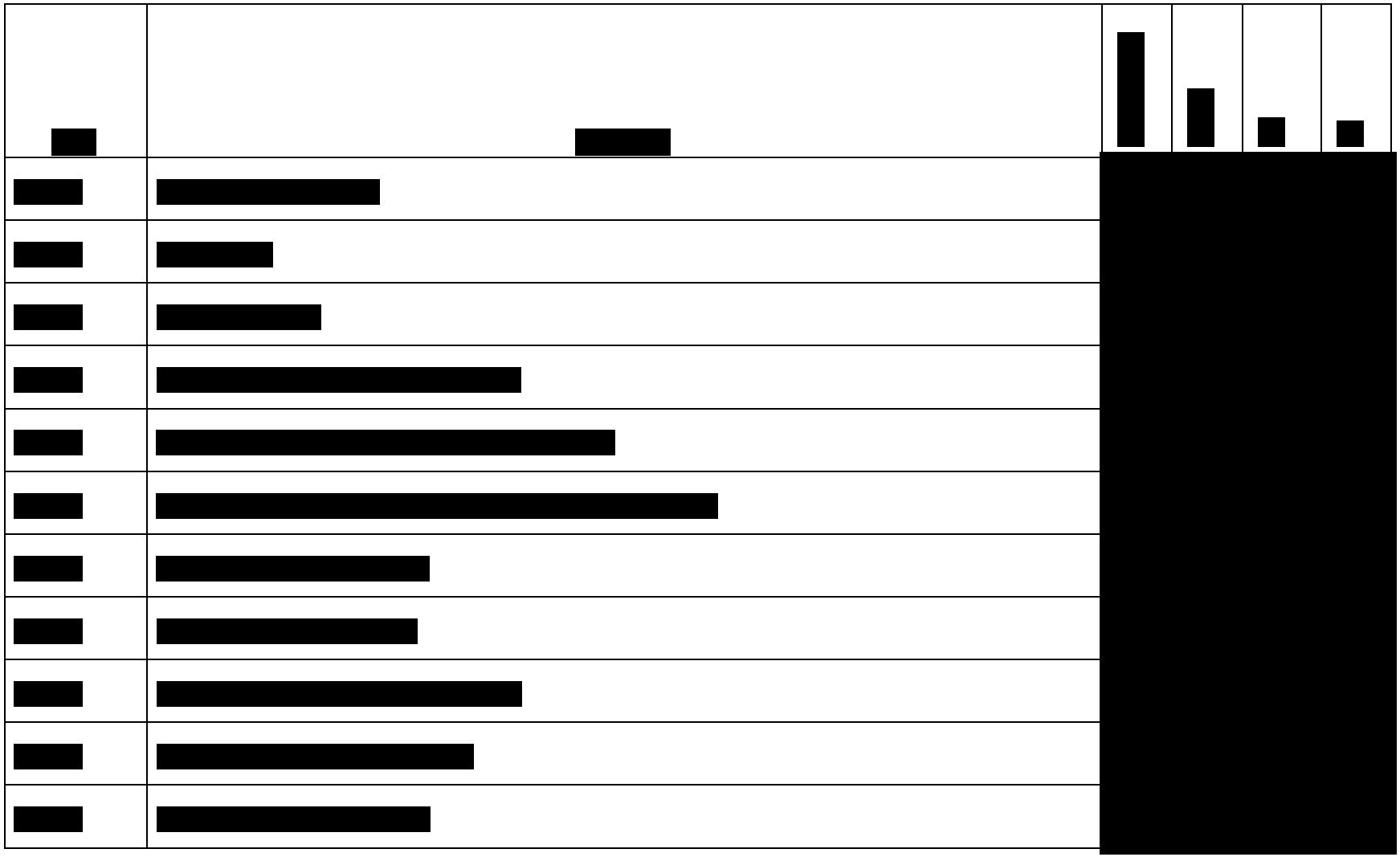

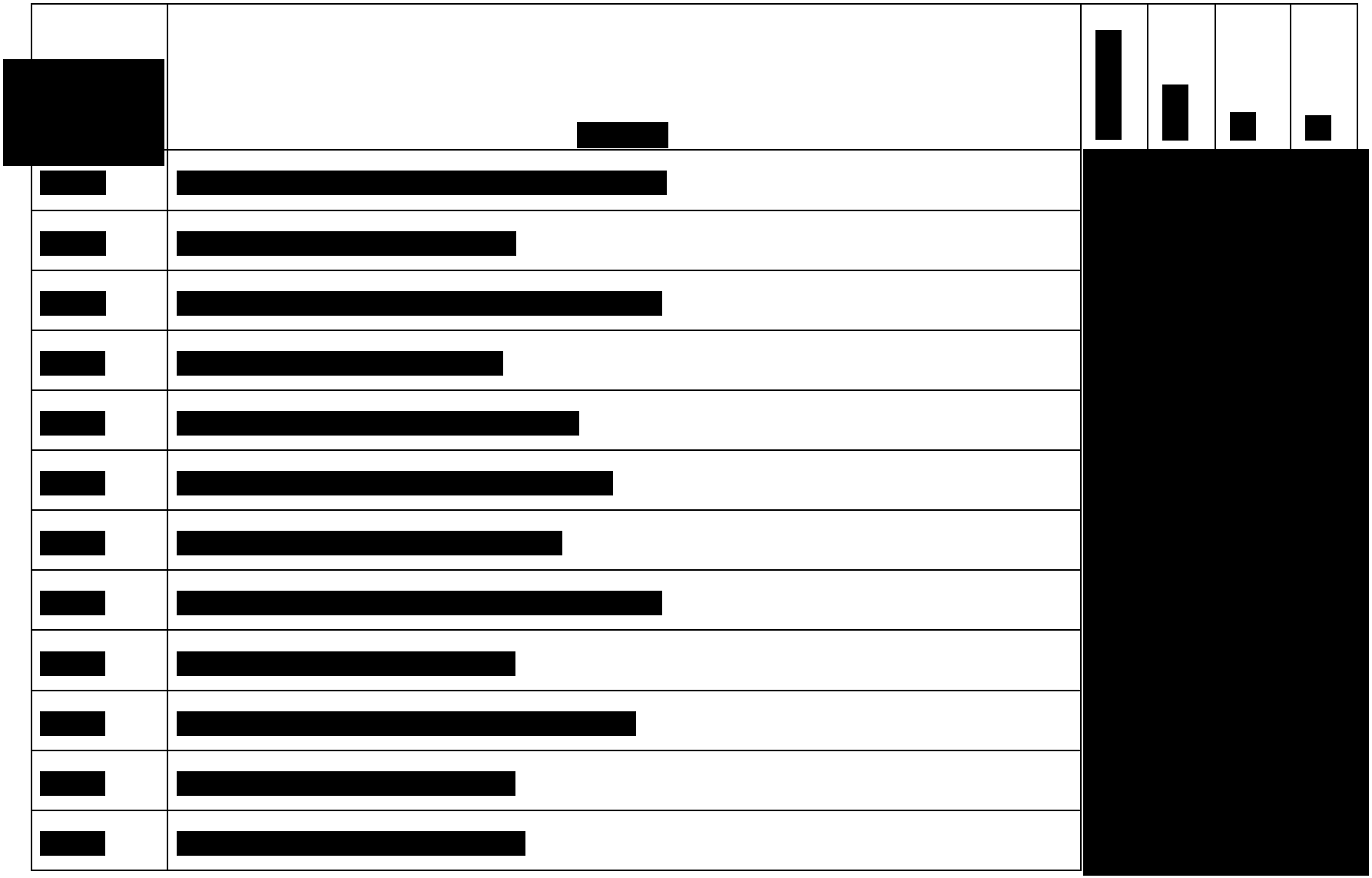

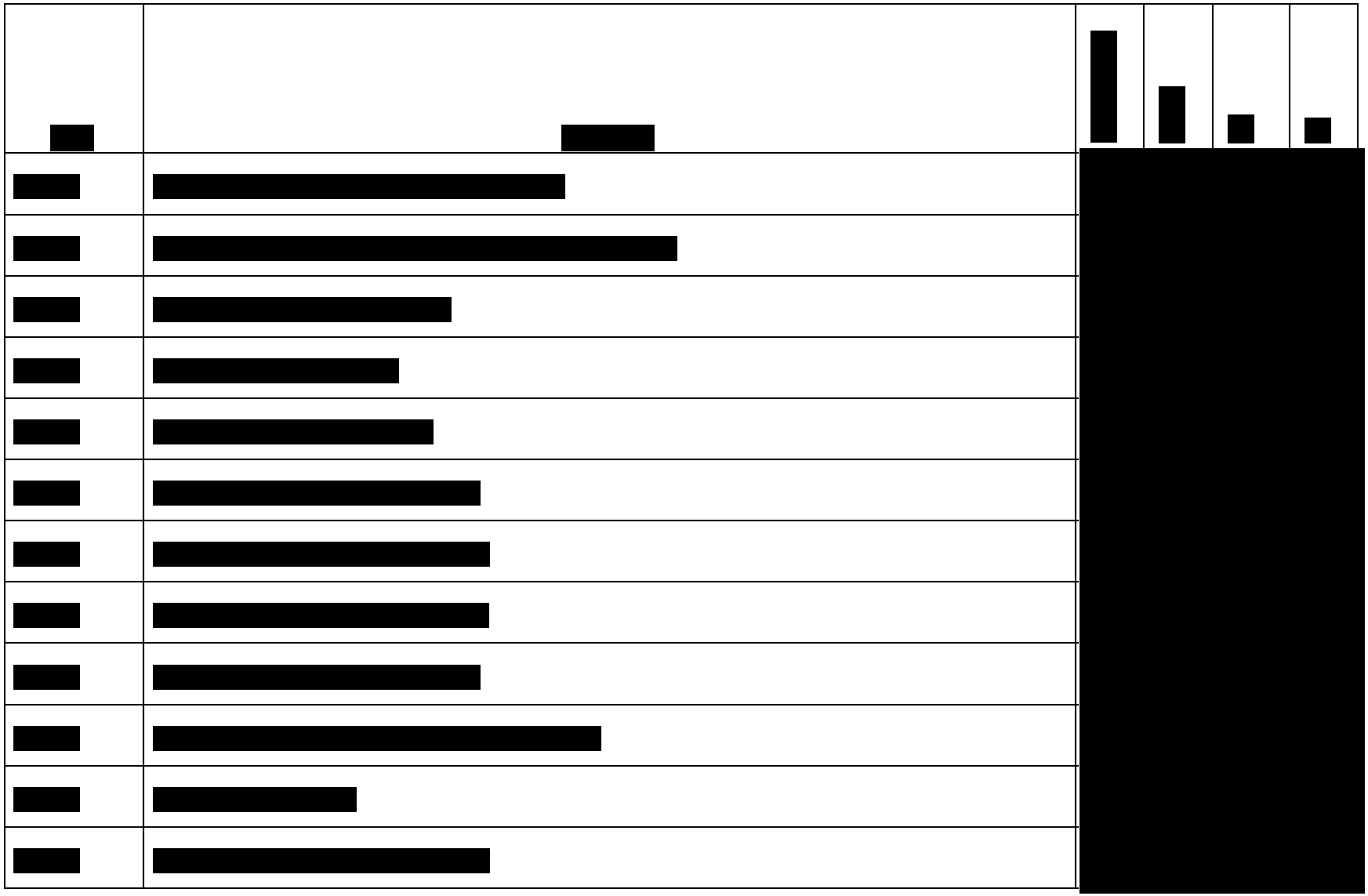

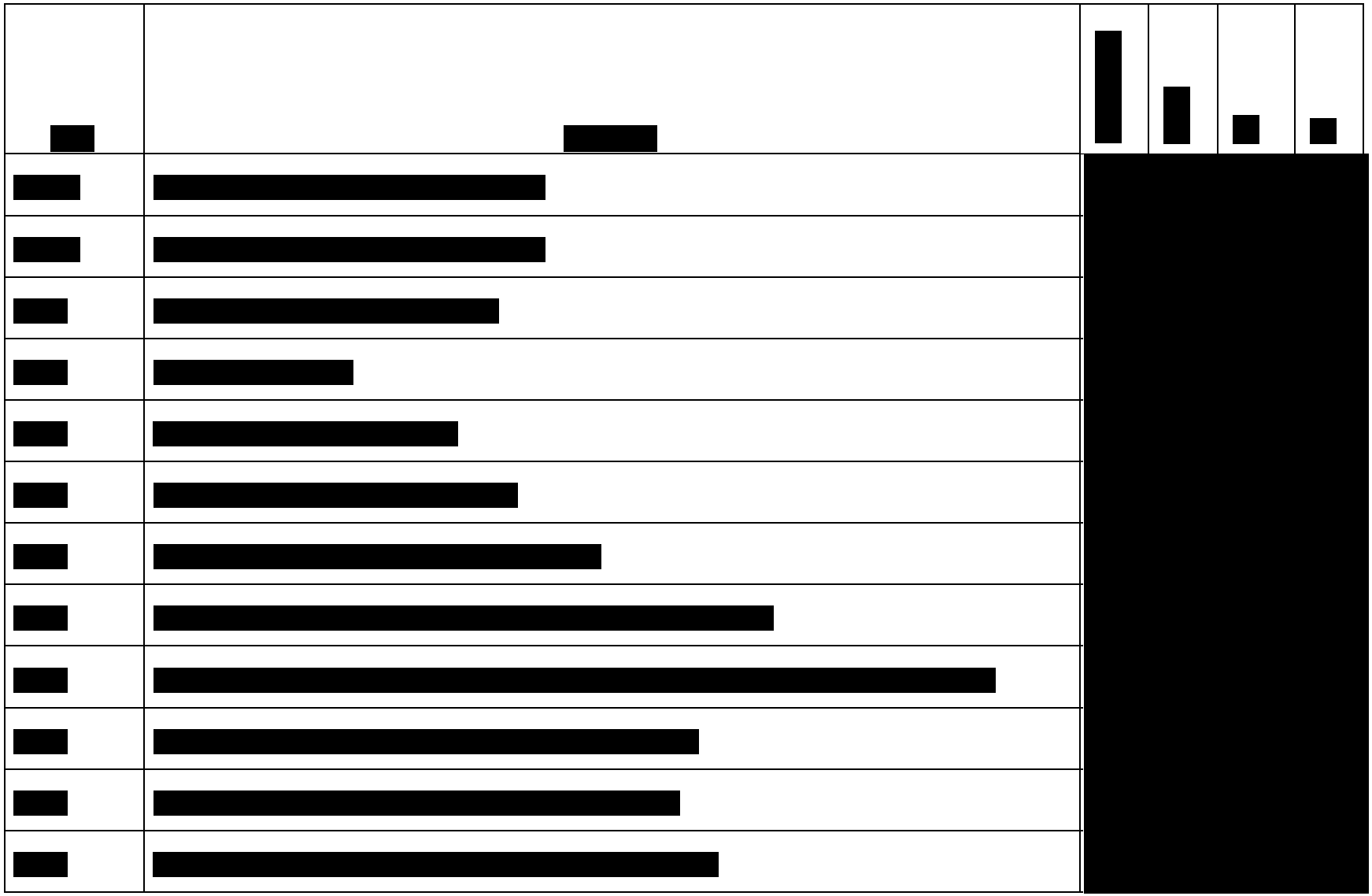

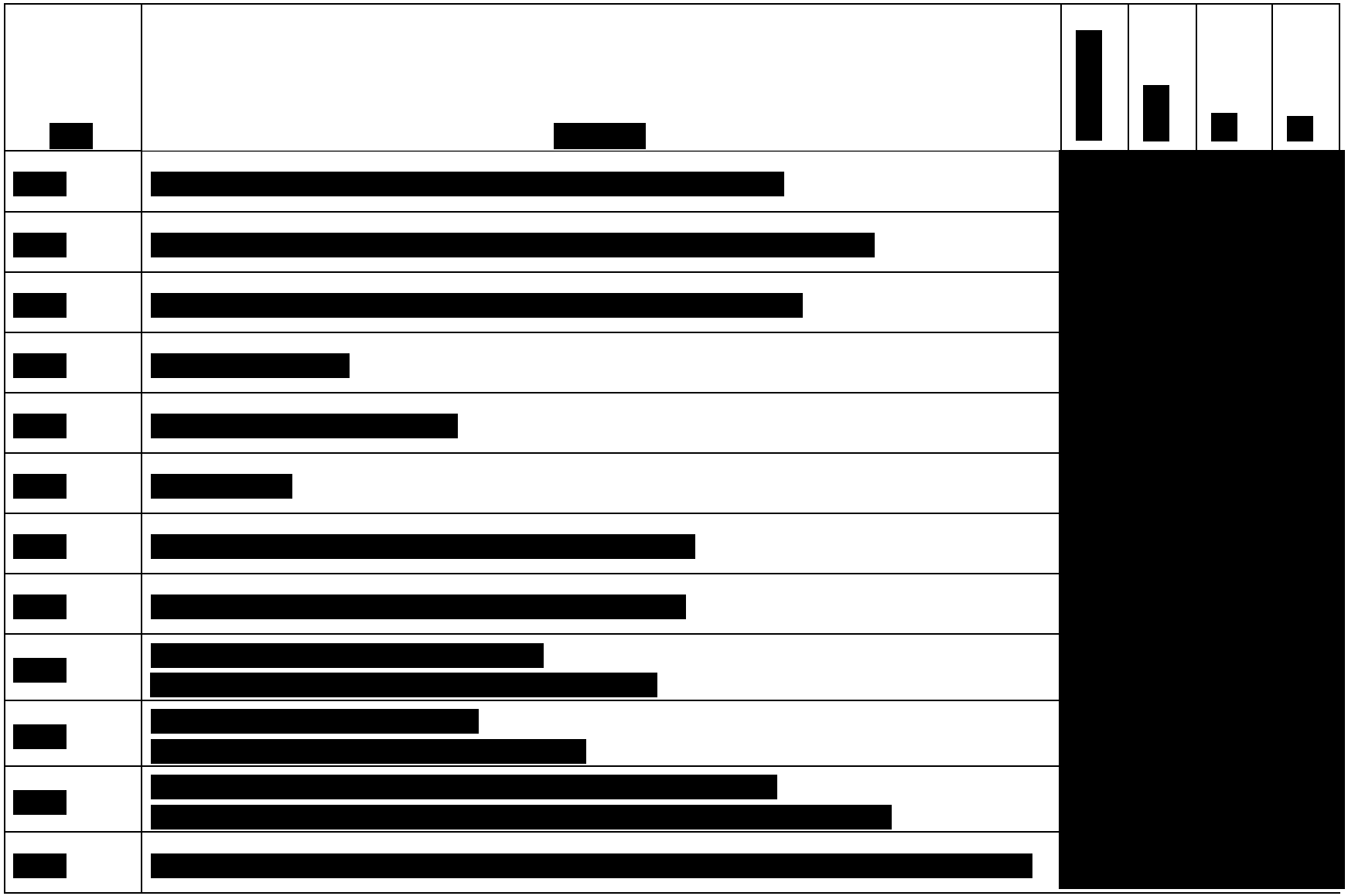

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